

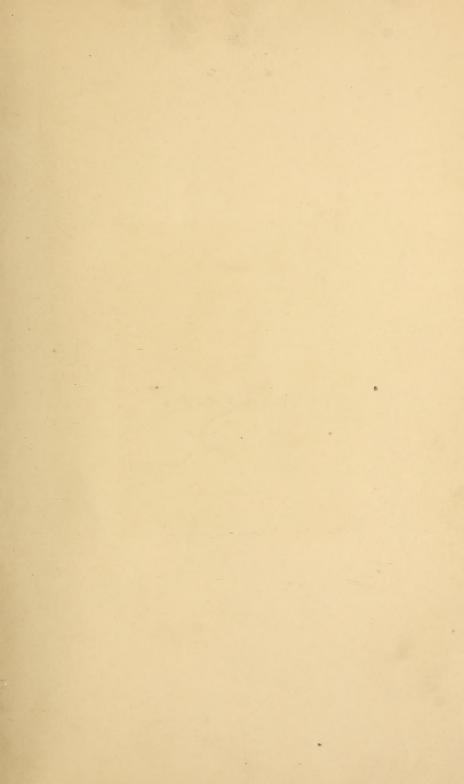


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## A GUIDE

TO THE

# CLINICAL EXAMINATION

OF

# THE BLOOD

## FOR DIAGNOSTIC PURPOSES

RICHARD C. CABOT, M.D.

WITH COLORED PLATES AND ENGRAVINGS

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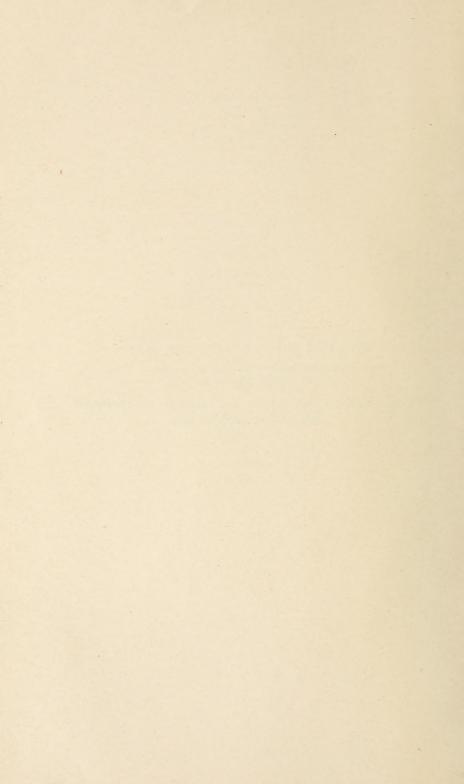


COPYRIGHT, 1901, BY WILLIAM WOOD AND COMPANY. TO

## WILLIAM SIDNEY THAYER, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE IN JOHNS HOPKINS UNIVERSITY,

IN GRATEFUL RECOGNITION OF THE STANDARD OF THOROUGH WORK ESTABLISHED BY HIM.



## PREFACE TO THE FOURTH EDITION.

This book becomes with each succeeding edition more indebted to the labors of the internes of the Massachusetts General Hospital and less my book. Of the twelve thousand observations on which it is now based, less than three thousand represent my own work. The remainder I owe to the generosity of the visiting physicians of the hospital and to the zeal and skill of their internes. As the details of the technique employed have been substantially the same throughout the whole body of data, they form a single group superior in bulk and in detail to any elsewhere recorded. Our twenty-eight hundred observations in one thousand cases of typhoid fever are an example of the wealth of statistical data on which the conclusions of the book are based.

The text has been almost entirely rewritten. The section on serum diagnosis has been abridged and the table of contents abbreviated so that in spite of so many pages of new matter the book is not greatly increased in size. The most extensive changes are in the sections on pernicious anæmia, leukæmia, typhoid fever, and the diseases due to animal parasites. I have profited largely from the magnificent work of A. E. Taylor on leukæmia, the extensive observations on typhoid analyzed by Thayer, and Ewing's studies in malarial parasitology.

190 Marlborough Street, Boston.

August, 1901.



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BOOK I.



## INTRODUCTION.

#### SCOPE AND VALUE OF BLOOD EXAMINATION.

Hæmatology has now established for itself a definite field of usefulness in the practice of medicine. It has solved some problems where least was hoped from it, and given us disappointingly little help where great expectations had been aroused. We might have expected from it some light on the nature of rheumatism, furunculosis, uræmia, diabetes, but none has come.

On the other hand, who could have hoped that it would help us in the diagnosis of central pneumonia, of deep-seated suppurations, and of trichinosis, or in the prognosis of relapsing fever or of pneumonia?

There are probably not more than five or six diseases in which the blood examination gives us the diagnosis ready-made, but there is a very considerable number of conditions in which the blood examination will help us to make it. Not pathognomonic signs, but links in a chain of evidence are what we are to expect from blood examination. Very often the simple discovery that the blood is normal may be a fact of the greatest value in diagnosis.

On the whole it seems to me that the examination of the blood gives evidence similar in kind and not much inferior in value to that obtained by examination of the urine. Both methods of examination give us (a) a ready-made diagnosis in a few diseases; (b) side lights on a good many obscure conditions; and (c) the frequently great assistance of a negative report. In certain wards of the Massachusetts General Hospital it has been for some years the rule to examine the blood of every patient as a matter of routine at the time of entrance. In a small proportion of cases this gave negative evidence only; in a much larger proportion it materially assisted in the making of a diagnosis.

Improvements in technique have lessened the labor and increased the accuracy of blood examination. The most important facts

about the blood of nearly every case can be obtained by a practised observer in fifteen minutes.

The blood is the only tissue that we can study easily during the life of the patient. Its relations to all other tissues are such that it is typical of them all in a way that no other tissue is, acting on all and being acted on by all. As yet we have studied chiefly its morphology, and from that single aspect obtained most of the clinically valuable information which we possess about it. But the field of the blood chemistry is in many respects even more promising at the present time, and there seems reason to believe that the study of the blood is still in its infancy and will take a higher place in the future as an aid to diagnosis, prognosis, and treatment.

Like all methods of physical examination it has especial usefulness when we cannot communicate with a patient, either by reason of his unconsciousness, stupidity, or insanity, or because he speaks no widely used language. In such cases the detection of marked anæmia, leucocytosis, eosinophilia, a typhoid serum reaction, or a malarial organism may be of great assistance. Malingering is made more difficult by it, and in the differentiation of organic from functional disease it is often very helpful. There is no febrile disease on which it may not throw light.

The evidence for these and many other aids furnished by the blood examination in clinical work is given in the later chapters of this work.

## PART I.

## METHODS OF CLINICAL EXAMINATION OF THE BLOOD.

#### CHAPTER I.

Confining ourselves to the clinically available processes by which we can gain information of diagnostic or prognostic value, blood examination at the present time embraces the following processes.

- 1. Estimation of the total volume of the blood and of its oxygen capacity.
- 2. Examination of the fresh blood (with or without a warm stage).
  - 3. Counting the red and the white corpuscles.
  - 4. Estimation of the amount of coloring matter.
  - 5. Examination of dried and stained specimens.
  - 6. Bacteriological examination of the blood.
  - 7. Examination of the serum.
  - 8. Estimation of the coagulation time.

Less important are:

- 9. Estimation of volume of corpuscles and of plasma in a given quantity of blood.
  - 10. Estimation of the specific gravity of the blood.
  - 11. Estimation of the number of blood plates.
  - 12. Estimation of the amount of fibrin.

To describe these processes in detail is the purpose of the next chapters.

#### I. ESTIMATION OF THE TOTAL VOLUME OR MASS OF BLOOD.

Until the present year the determination of the total mass of the blood has been practically beyond our reach, and our blood examinations have dealt wholly with small "samples" drawn from the

<sup>1</sup> See Chapter xiii. of Book II.

periphery and treated as typical of the rest without regard to any possible variations in the total amount of blood in the vessels.

But recently Haldane and Smith, in three important and interesting papers, have suggested and applied a method which, if it stands the test of time and criticism, will add very materially to our knowledge of blood physiology and blood pathology.

The essential features of their method are as follows:

- 1. The patient inhales a measured volume of CO (a harmless and not unpleasant process). After two or three minutes a few drops of blood are taken for analysis and the percentage to which the hæmoglobin has become saturated with carbonic oxide is estimated (by the carmine method, see reference at foot of page).
- 2. Knowing the amount of CO inhaled, and the degree in which the blood has become saturated by this known amount, the quantity of CO capable of being taken up by the whole of that patient's blood can be calculated. Thus, supposing that the volume of carbonic oxide delivered was 150 c.c., and that the blood was twenty-five per cent saturated, it is obvious that the blood would have been one hundred per cent saturated by 600 c.c. Its total capacity for CO (or for oxygen) is 600 c.c.
- 3. How then shall we connect this estimate of total oxygen capacity with the volume of the blood? In a previous research the writers showed that the oxygen capacity per 100 e.c. of any given sample of blood can be accurately estimated by comparing its color with the color of an equal sample of ox blood whose capacity for oxygen has been previously determined. For example, a patient having absorbed 100 c.c. of CO, it is found that his blood is one-fifth saturated by this gas. The total capacity for CO (and so for oxygen) is therefore 500 c.c. But further, the patient's blood is found to have the same color as an ox's blood every 100 c.c. of which has been previously determined to be capable of taking up 20 c.c. of oxygen. The patient's total oxygen capacity (500 c.c.) divided by the oxygen capacity of every 100 c.c. of his blood (20) gives us 25. This figure is then the number of hundreds of cubic centimetres of blood in his body—2,500.

Smith has now applied this method to over one hundred cases, and found it to produce no appreciable ill-effects on the patient. As the result of these studies, he estimates the average volume of

<sup>&</sup>lt;sup>1</sup> 1. Journal of Physiology, xxii., p. 232. 2. Journal of Physiology, p. xxv., 331. 3. Transactions of the Pathological Society, 1900, vol. li.

blood in health as 3,240 c.c. or 3,420 gm. The latter figure is obtained by means of the average specific gravity of normal blood (taken as 1.055). In the fourteen normal cases studied the blood mass varied from 2,830 to 4,550 gm. or  $\frac{1}{30}$  to  $\frac{1}{16}$  the body weight, but was never as large as had previously been estimated  $(\frac{1}{30})$ .

In chlorosis, Smith found that the apparent diminution in hæmoglobin was, in fact, due to the great increase in the plasma of the blood (serous plethora), the total oxygen capacity or hæmoglobin remaining normal. In pernicious anæmia, on the other hand, the amount of plasma is sometimes increased and sometimes diminished, but the oxygen capacity or hæmoglobin is always low. These observations will be referred to again later (see p. 131).

#### II. EXAMINATION OF THE FRESH BLOOD.

(a) Puncture.—In all the processes about to be described (except the bacteriological examination) the first step is as follows:

Gently cleanse the lobe of the patient's ear with a damp cloth and then dry it. All vigorous rubbing or kneading is to be avoided. Attempts to sterilize the skin or to cleanse it with alcohol and ether are a waste of time. A small lancet or a bayonet-pointed surgical needle may be used; a sewing needle gives more pain and draws less blood from a given depth of puncture. A steel pen, with one nib broken off, makes a good lancet. The needle need not be sterile. In several thousand blood counts made at the Massachusetts General Hospital since 1893 the needles have never been sterilized and no signs of sepsis have been seen in any case.

Possibly this is due in part to the fact that the next step in the process after the puncture has been made is always to wipe away four or five successive drops as they emerge. This serves not only to get the blood flowing freely, but also to wash the ear in its own blood.

The puncture is best made into the lower surface or edge of the lobe, which is steadied with the fingers of the left hand. A very quick stroke gives least pain, the hand rebounding like a piano hammer. If the skin of the lobe is stretched tight with the fingers of the left hand so that no "give" is possible, the quick puncture gives hardly any pain. I have repeatedly taken blood from a sleeping child without waking it. What hurts the patient is the mistaken tenderness that slowly presses the needle through the skin.

The puncture must be deep enough to make the blood flow freely and without pressure, after it is once started by pressing out a few drops. Blood squeezed out with pressure should never be used for counting, as it may be considerably diluted with fluid pressed out of the neighboring tissues. If the skin is moderately thin and the ear easily made hyperæmic, a puncture one-eighth of an inch deep is sufficient. With thick, bloodless skin it may be necessary to go in one-quarter or one-third of an inch—never more. Beware of bleeders. I have seen bleeding from a puncture made for a blood count which could not be checked for three-quarters of an hour. It is always safer to ask after a history of hæmophilia as a matter of routine before taking blood, just as one asks after false teeth before etherizing. If there is a history of hæmophilia, a mere touch of the needle point will give us all the blood we need without embarrassing us with a troublesome hemorrhage.

There is no question as to the superiority of the ear over the finger for drawing the drop. The ear is less sensitive than the finger, and a slighter puncture gives us all the blood we need. Moreover, it is a distinct advantage, especially in children, that the patient cannot watch the puncture of the ear, or the preparations for making it, and cannot easily withdraw the part. A sleeping patient often needs to be roused to get at his finger, while his ear is usually easily accessible above the bed clothes. Again, the absence of any bony prominence against which to press makes us less likely to use too much pressure than if we puncture the finger.

When one is making frequent examinations of the blood of a sensitive person, as in pneumonia, these details are of real importance, and in cases of pernicious anæmia in which the previous attempts to get blood from the finger had been absolute failures, I have found no difficulty in getting it from the ear. In this disease the advantages of the ear over the finger are peculiarly great.

## Preparation of Temporary Specimens for Immediate Examination.

(b) When, after wiping away the first four or five drops, a good-sized drop exudes spontaneously, touch the centre of a perfectly clean cover-glass against the summit of the drop without touching the skin itself at all, and drop the cover-glass face downward upon a slide so that the force of the impact will help to spread the drop of blood thinly and evenly between slide and cover. It is recommended by Ehrlich and others to hold the cover-glass with forceps,

but there is no harm in holding it with the fingers, provided we avoid touching either of its surfaces, *i.e.*, hold it always as in Fig. 1.<sup>1</sup>

Slide and cover must be perfectly clean, else the blood will not spread out in a layer thin enough to avoid the corpuscles overlying

each other so that not one of them is clearly seen. Further, as dirt simulates fairly closely some of the pathological appearances for which we are on the lookout, its presence on the slide leads to loss of time or to mistaken conclusions. Coverglasses, as they come from the shops, may be coated with a substance not easily to be removed. To get them really clean nothing is so simple as or more effective



Fig. 1.—Proper Method of Holding a Cover-glass.

than soap and water. After several years' use of the method of cleaning usually advised (viz., strong mineral acid, followed by alcohol and then by ether), I have become converted to the use of plain soap and water as the best and simplest way of cleaning slides or cover-glasses. Rub soap over every part of the glass, wash it off with water, and polish it thoroughly with a clean handkerchief (most towels are apt to leave a scrap of lint on the glass).<sup>2</sup> If slide and cover are perfectly clean, are held as in Fig. 1, and allowed to touch only the summit of the blood drop and not the skin, the blood will spread out properly between them, and no pressure on the cover-glass will be needed to make the layer of corpuscles thin enough. Pressure is undesirable, as it often makes all sorts of artefacts in the preparation and hastens crenation of the red corpuscles. Better results are obtained if slide and cover are warmed just before using, and it is well to have an assistant rub the slide vigorously with a towel just before it is used.

This method is, of course, applicable only to specimens to be

<sup>1</sup> I am not unmindful of Ehrlich's warning that the moisture of the fingers spoils the specimen; but in practice I do not find it to be true except as regards the margin of the film, the good preservation of which is not essential. Only the thinnest cover-glasses in the market should be used,  $\frac{\tau}{8}$  inch is the best size.

<sup>2</sup> Further experience has convinced me that water alone is generally sufficient, provided the polishing, which is the chief factor of success, is thorough. Tissue paper is very useful for polishing cover-glasses. After polishing, it is well to pass them through a Bunsen or alcohol flame once or twice.

immediately examined. Specimens which are to be transported or preserved should be prepared as directed on p. 43.

## Prevention of Cell-Death.

Slides so prepared are usually best examined with a one-twelfth oil-immersion lens. As a rule they keep long enough for purposes of examination without any further precautions, but if we desire to keep the blood fresh and uncoagulated for a longer period, it is best to exclude air in this way: Paint upon the slide with vaseline, cedar oil, or any gummy substance a hollow square or ring of about the size of the cover-glass, so that when the latter with its drop of blood is put down upon the slide the drop will spread out inside the ring of oil, which seals the margins of the cover-glass to the slide. Specimens so prepared will keep for many hours unchanged, and without crenation or coagulation, if the weather is warm or if the slide be kept in a warm place.

In examining blood suspected of containing malarial parasites it is sometimes useful to put the whole microscope into one of the warming apparatuses devised for the purpose. This is better than any of the various kinds of warm stage in use, but in clinical work there is rarely if ever any need for artificial heating apparatus of any kind, provided the room and the slide are warm.

## What Can be Learned from Fresh Blood.

In the first place we note the readiness or sluggishness of its flow from a puncture of standard depth. The blood flows more readily than usual in the following conditions:

- 1. Peripheral congestion or vaso-dilatation.
- 2 Exaggerated fluidity of the blood (chlorosis, some types of anæmia, and hæmophilia).

It flows sluggishly:

- 1. After profuse hemorrhage or serous drain (cholera).
- 2. In certain cases of extreme anæmia— $e\ g$ , emaciated cancer cases.
- 3. Vasomotor spasm (cold, hysteria, Raynaud's disease, uræmia—certain cases).
  - 4. Exaggerated coagulability

Examination of the fresh blood by the method described above

is also the best way known for ascertaining the presence or absence of—

- 1. The Plasmodium malariæ.
- 2. The Spirochæte of relapsing fever.
- 3. The Filaria sanguinis hominis.
- 4. Rouleaux formation among the red cells.

It is also a quick and convenient method of finding out with approximate accuracy:

- (a) Whether the blood contains an increased amount of fibrin;
- (b) Whether any considerable anæmia or leucocytosis is present;
- (c) Whether or not the amount of hæmoglobin in the red cells is much decreased;
  - (d) Whether the red corpuscles are deformed;
- (e) Whether the "blood plates" are increased or not. A practised observer can also make a diagnosis of leukæmia by this method in most cases, but here mistakes may easily occur.

So much can sometimes be learned from a specimen prepared in this very quick and easy way that it should be as much a matter of routine as a urine examination. But in order to get any information from such a preparation we must previously have familiarized ourselves with the appearance of normal blood under such conditions—with the size, shape, color, and refractions of the red cells, white cells, and blood plates and their ratio to one another, and with the great variety of curious phenomena to be seen as a drop of blood gradually dries up between slide and cover. No book can teach this; it must be learned by actual experiment.

Some of the commoner sources of error will be referred to later. Here I will mention only the Brownian movement in the protoplasm of the corpuscles, to be distinguished clearly both from the amœboid movements of the leucocytes or of the malarial parasite and also from the irregular contractions of the dying protoplasm, which give rise to pseudo-amœboid motions in the crenated points of normal red cells or in the irregular projections of corpuscles deformed by disease (vide infra).

For a more detailed description of normal red corpuscles, white corpuscles, and blood plates the reader is referred to Part II.

An account of the pathological changes to be observed in the fresh blood will be given in later chapters.

<sup>1</sup> More accurately it is only the ratio of red to white corpuscles that we can determine, and when the red are very much diminished in number we may be deceived into supposing that the white are increased.

### CHAPTER II.

#### COUNTING THE CORPUSCLES.

- I. The Thoma-Zeiss counter.
- II. Durham's modified counter.

I. Out of the many instruments devised for this purpose that of *Thoma - Zeiss* with Zappert's modified ruling of the counting

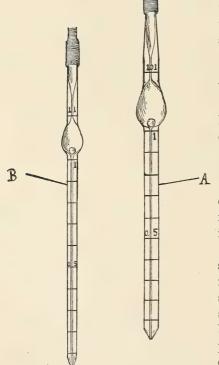


Fig. 2.—Thoma-Zeiss Pipettes. A. For red corpuscles; B, for white corpuscles.

chamber is the best, and much the most commonly used. In the use of this instrument there are five steps or stages:

- 1. Puncturing the ear.
- 2. Diluting and mixing the blood thus obtained.
- 3. Adjusting a drop of diluted blood in the counting chamber.
  - 4. Counting the corpuscles.
  - 5. Cleaning the pipette.

To count the white corpuscles, an instrument different from that employed for the red is often used.

The technique is nearly the same for both instruments, but for clearness' sake I shall describe them separately. To save time I shall call the small-bore pipette used for red corpuscles (Fig. 2, A) the "red counter," and the large-bore pipette (Fig. 2, B) the "white counter."

#### COUNTING THE RED CORPUSCLES

(a) After puncturing the ear as above described, and as soon as the blood is flowing freely, put the point of the "red counter" into the drop as it emerges from the ear, and by sucking gently on the rubber tube attached to the other end, draw up blood to the mark

0.5 on the pipette. It is convenient to rest the end of the pipette on the thumb as shown in Fig. 3. It needs some practice to stop exactly at the mark, but if we happen to draw the blood up a little past the mark 0.5 no considerable error results, provided we draw the column down again to the mark by tapping the point of the pipette on a towel, and provided also that the instrument is perfectly clean and dry. The aim and intention, however, should always Fig. 3.—Method of Resting Point be to stop exactly at the mark 0.5, and with a little practice we can do it, except with



of Pipette on the Thumb while Sucking in Blood.

nervous or delirious patients, and those who carelessly move the head just at the critical moment. With such patients we usually have to content ourselves with drawing the blood a little beyond the mark 0.5 and then drawing it down again to the mark as above described.

## Diluting the Blood.

(b) The bottle of solution to be used for diluting the blood should be ready uncorked at the bedside. Of the many solutions suggested by various authors none is better than Gower's, the formula for which is as follows:

Sodii sulphat	gr. 112
Acid. acet	3 v.
Aquæ	Ziv.

Toisson's solution is also very useful and stains the white corpuscles so that they can be easily distinguished from the red. composition is as follows:

Methyl violet, 5 B	0.025 gm.
Sod. chlor	1.000 "
Sod. sulph	8.000 "
Neutral glycerin	
Aquæ destill	160.000 "

We must wait about ten minutes after mixing before the leucocytes are fully stained. Except for this delay, the only objection to this solution is that it is rather difficult to clean the pipette after using it. If the white cells are counted with another pipette the staining fluid can be as well dispensed with.

Into a bottle of one of these solutions, ready at the bedside, the point of the pipette is to be plunged as soon as the blood has been drawn up to the point 0.5 and the outside of the pipette wiped clean of blood. Suction is then exerted through the rubber tube the instant the point of the pipette is below the surface of the diluting This suction is continued until the diluted blood has filled the bulb of the pipette and gone past it up to the point marked 101. It is not difficult to stop at this point, provided the pipette is perfectly clean and dry inside. Otherwise it is impossible. Should any mishap occur at this point, the whole process must be begun over again after carefully cleaning and drying the pipette. If no accident happens and the mixture is sucked up to and not past the mark 101, we have diluted the blood with two hundred times its bulk of neutral solution. If, instead of drawing the blood up to the mark 0.5, we draw it as far as the point marked 1, and then dilute as above described, the mixture will be 1 to 100. Some observers habitually use this dilution. The objections to it are (1) That if the blood is accidentally drawn up too far (i.e., past the mark 1) we cannot draw it down again but must painfully clean and dry out the pipette (see below, p. 18) and repeat the process. (2) If the blood contain approximately the normal number of corpuscles, they will be so crowded when adjusted on the ruled surface of the disc A that it is more difficult to count them. use another pipette for the white corpuscles, the dilution of 1:100 has no advantage to counterbalance these drawbacks.

While sucking in the diluting solution, it is well to roll the pipette on the long axis with the fingers of the hand which holds it in the diluting fluid. This mixes the blood instantly and prevents any of it from floating on the top of the solution and thereby coming up undiluted into the narrow portion above the bulb of the pipette, where it might possibly escape thorough mixing.

Next we thoroughly mix the blood and diluting fluid by shaking and rolling the pipette, its ends being closed by the fingers. The

<sup>&</sup>lt;sup>1</sup> Care must be taken that no saliva finds its way through the rubber tube and into the pipette. Never blow through the rubber tube.

little glass ball within the bulb helps this process materially. A minute's brisk rolling and shaking is as good as five minutes', as I have convinced myself by many experiments, and the distribution of the corpuscles throughout the mixture is very even, provided there is no delay in proceeding to the next step, 'viz.:

(c) Adjusting a Drop of Diluted Blood in the Counting Chamber.

—Remove the rubber tube from the pipette and blow out the portion of diluting solution which last entered the pipette, and which consequently has not been thoroughly mixed with the blood in the bulb. Five or six drops should be blown out before any is used for examination. Next put upon the surface of the counter (A, Fig. 4) a drop of such size that when the cover-glass (B) is let down

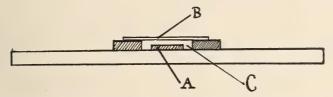


Fig. 4.—Thoma-Zeiss Counting Slide. A, Ruled disc; B, cover-glass; C, moat.

over it, the whole of the disc A is covered with the drop without any being spilled into the "moat" (C) around it. Just how large such a drop should be, can be learned only by practice. It is not literally necessary that exactly the whole disc A should be covered, provided nine-tenths of it is covered, but any spilling over into the "moat" (C) entails serious error.<sup>2</sup>

After the cover-glass has been let down upon the drop, we should be able (provided the whole instrument is *clean*) to see concentric rainbow rings between the cover-glass and the body of the instrument. These are known as Newton's rings. A little pressure with a needle on the cover-glass will often bring them out if they do not at once appear, but they must remain visible after the pressure is taken off. Otherwise we know that there must be some dirt or dust under the cover-glass preventing its settling exactly

<sup>1</sup> If we have to pause before going on to the next step, we must take care to roll and shake the pipette again when ready to proceed.

<sup>2</sup> In accordance with Meissen's suggestion Zeiss now supplies this apparatus with a groove in the glass disc outside the "moat," whereby communication is established between the latter and the external air. Thus the results of counting are made independent of differences in atmospheric pressure.

into position, and this will cause error in the count, though not a very considerable error in most cases. (To see Newton's rings we should get our eyes near to the level of the counting chamber so that the light from window or lamp is reflected from the surface of the cover-glass).

If the above conditions are not all fulfilled, the instrument should be washed and another drop tried, after shaking the pipette and blowing out a few drops as before.

The cover-glass must be let down as soon as possible after the drop has been put on the disc A, and before the corpuscles have time to settle. It is best to let it down with a needle as in mounting microscopic specimens.

## Counting.

(d) After waiting two or three minutes so that the corpuscles may settle thoroughly upon the space ruled off on the disc A, the

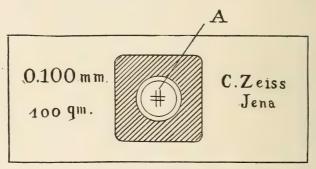


Fig. 5.—Thoma-Zeiss Counting Slide. A, Ruled disc.

counting is begun, using preferably an objective 5 of Leitz or D of Zeiss and a No. 1 or 2 eyepiece.

The central part of the ruled space on the surface of Zappert's counting chamber (A, Fig. 5) is divided into four hundred squares, every group of sixteen squares being enclosed in double lines to make it easier to know how many squares we have counted (see Fig. 6). Including the squares with double lines we have a group containing thirty-six small squares, a group convenient to count at one time as it just about fills the field of the objective Leitz No. 5, or Zeiss D with a No. 2 eyepiece.

To avoid considerable error we should count the corpuscles in five fields of thirty-six squares each, such as is shown in Fig. 6, taking the fields in various parts of the whole ruled space. The instrument should then be washed ' and the whole process repeated with a second drop. If the count of the second drop differs widely from that of the first, a third drop should be counted, and the average taken of those two which are most nearly alike. Thus at least three hundred and sixty small squares should be counted; with such a number the error is not over three per cent for practised observers. In normal blood this means counting about 2,160 corpuscles, as six

or seven to a small square is about the normal average when we are using a dilution of 1:200 such as has been described (twelve to fourteen cells per square in a dilution of 1:100).

Among the difficulties encountered in counting is the presence of a few corpuscles on or touching one or more of the lines bounding the space to be counted. Shall we count these out or in?

In counting, for instance, a field like that in

A						C					
D	00	000	000	000	000	00	000	0	0	0	
<i>D</i>	000	0	0	000	00	0 0	000	0	0	0	U
	00	0	0		00	000	00	0	0	000	
,	000	00	0,0	00	000	000	0 0	0 0 0	0 0	00	
	000	0 0	000	000	000	000	000	00	000	00	
	900	0 0	0 0	000	000	000	000	000	0	000	
_	000	0 0 0	0	000	000	000	000	000	0	000	
	00		0	00	000	000	00		00	0	
В	0	0		00	0.0	0 0	.000	00	°	00	D
Ь	0 0	0 0	0	000	000	000	0000	300	0	000	В
A											
Fig 6 - Field of Thirty-giv Squares on Ruled Disc of											

Fig. 6.—Field of Thirty-six Squares on Ruled Disc of Thoma-Zeiss Counter Covered with Normal Blood Diluted Two Hundred Times.

Fig. 6, what are we to do with the cells which sit astride the lines AA, BB, etc.?

To get round this difficulty, it is best to make it a rule to count in all the corpuscles on or touching some two of the boundary lines (e.g., AA and BB) and to take no notice of any cell on or touching the lines CC and DD. In this way the exclusions just balance the inclusions. Of course all cells within these outer boundary lines are to be counted whatever their position.

Beyond this the details must be settled by each man for himself. My own habit is to count through the squares in the order indicated by the track of the serpentine arrow in the accompanying Fig. 7, and to count by twos or threes.

<sup>&</sup>lt;sup>1</sup>Use only water—alcohol dissolves the cement which holds the ruled disc in place.

<sup>&</sup>lt;sup>2</sup> See Reinert's "Zählung der Blutkörperchen," Leipzig, 1891, p. 48 et seq.

A movable stage makes the counting easier, especially for beginners. Either natural or artificial light may be used, with a small aperture diaphragm, and if the instruments are clean and the diluting solution fresh and free from sediment, there is no difficulty in deciding how many cells each square contains, and no ex-

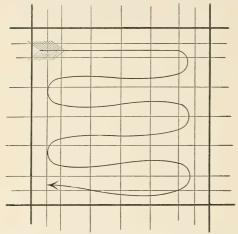


Fig. 7.—The Arrow Indicates the Order in which the Squares are Counted.

traneous fragments to be excluded. We must distinguish the white corpuscles from the red, not by their size but by their stain if Toisson's solution is used, otherwise by their peculiar shining look when the lens is drawn up so as to put the red cells slightly out of focus. The blood plates are not noticeable and lead to no errors

When the number of corpuscles in 360 squares has been counted the

number is divided by 360 and multiplied by 800,000 (i.e., by 200 to make up for dilution and then by 4,000, because each square is equivalent to  $\frac{1}{4000}$  of a cubic millimetre), which gives us the number of corpuscles per cubic millimetre.

These figures need not be committed to memory, for we have marked on the instruments used all the data necessary for the calculation, *i.e.*, the dilution figures on the pipette and the area and depth of a single square on the counting slide.

(e) The importance of cleaning the pipette as soon as the counting is done is so great that it should be reckoned as one of the regular steps on every count. First water, then alcohol, and lastly ether must be sucked into the pipette and brought into contact with every part of the bulb and tube. After this air must be sucked or pumped through the tube until it is perfectly dry and the glass ball will roll about freely in the bulb without sticking anywhere.

These precautions take but two or three minutes, and if they are

<sup>&</sup>lt;sup>1</sup> Most diluting solutions precipitate or accumulate spores, and need to be frequently renewed or filtered.

omitted and the blood dries in the pipette, it may take several hours' work to get it clean. Further, if it is not thoroughly *dried* after cleaning, the mixing of the blood when it is used next cannot be done accurately.

The first three steps of the above process (i.e., the obtaining, diluting, and mixing of the blood) must be done as swiftly as is compatible with accuracy, but when once the blood is mixed in the pipette it can be kept there indefinitely and counted at leisure. None of the corpuscles are destroyed or lost, and if the bulb is thoroughly rolled and shaken up whenever we are ready to count the blood, no error results from keeping it twenty-four hours or more in the pipette.

It is not necessary, therefore, to carry a microscope to the patient's house or bedside; the pipette and the diluting solution are all that we need to take with us, and when the blood is mixed in the pipette, the latter's ends can be closed with a rubber band, and the blood carried home and counted at leisure. The pipette should be kept approximately horizontal during the transit.

### COUNTING THE WHITE CORPUSCLES.

To make a reasonably accurate count of white corpuscles, using the "red counter" and the dilution of 1:100 or 1:200, we need to count an immense number of squares, far more than was necessary in estimating the red cells—in fact, at least ten times the whole ruled space. It is therefore far quicker and more accurate to use the "white counter" or large-bore pipette with a diluting solution which renders the red cells invisible and leaves only the white to be counted. Such a solution is the one-half of one-per-cent solution of glacial acetic acid in water. With this the white corpuscles stand out very clearly and the red can barely be seen at all. The technique is the same as that already described, with the following exceptions:

- 1. The drop of blood needed is nearly three times as large as that used in the "red counter"; it is about as big as can be made to stay on the ear without rolling off, even if we draw blood only to the mark 0.5. If we draw blood to the mark 1, as advised by Türck, we must make a deeper puncture and suck in the blood as it flows without waiting for the formation of drops.
  - 2. The bore of the tube being large, it fills and empties more

readily. Hence our suction must be gentler, and it is rather harder to stop exactly at the mark 11. For the same reason the diluted blood will run out of the pipette if the latter is not kept nearly horizontal, and the bottle of diluting solution should accordingly be tipped up as we plunge in the point of the pipette, so that the latter is depressed as little and for as short a time as possible before suction begins.

3. Zappert's modification of the Thoma-Zeiss counting chamber should be used. Zappert's counting chamber (now supplied by Zeiss at the same price as the ordinary one, i.e., 15 marks) differs from that ordinarily used in that the central square millimetre is surrounded by eight undivided squares of the same size (see Fig. 10). With this ruling one counts first the number of leucocytes in the central square (about 35 in normal blood) and then in each of the surrounding undivided squares. This gives us a total of about 300 leucocytes (in normal blood) as a basis for our calculations. The total so obtained is divided by 9, and then multiplied by 200 (provided we have diluted 1:20).

The advantages of the large-bore pipette are obvious. The only drawback is its expanse. The technique is not at all difficult.

## Counting Both Red and White Cells with the Same Pipette.

We may avoid buying both large-bore and small-bore pipettes in one of the following ways:

- 1. We can count both red and white corpuscles with the "red counter."
- 2. We can count both red and white corpuscles with the "white counter."

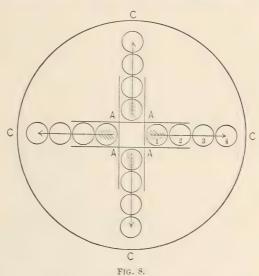
The reason why we cannot use the "red counter" for counting white cells, unless modified in some way, is that in the whole ruled surface of the counting chamber not more than three or four white corpuscles are to be found in normal blood when diluted two hundred times. If we dilute less, we cannot see the cells distinctly, because they are so crowded. If we find, say, three white corpuscles as the number to be used as a basis in calculating the number of white cells in a cubic millimetre, the chance of error is very great, the multiplier being so large (2,000) and the multiplicand so small (3).

To get over this difficulty we may utilize the cells spread over

the disc of the counting chamber outside the ruled space in one of the following ways:

(a) By measuring the field of the objective used. The writer's objective, No. 5 of Leitz, has a field of very nearly one-quarter of a square millimetre or one-quarter of the whole ruled space. Four fields of this lens, taken anywhere outside the ruled space, therefore, contain the same number of cells as will cover the whole four hundred small ruled squares, and when we have counted the white cells in a series of four fields of this lens, we have accomplished as much as if we have put a fresh drop upon the counting chamber and counted all the ruled squares over again; the latter process is

tedious, the former very quick. Thus it is my practice in some cases to proceed as follows (see Fig. 8): Supposing the large circle CCCC to represent the surface of the small disc (A, Fig. 4) in the centre of the counting chamber, and AAAA the ruled squares in the middle of this disc, four microscopic fields are taken in the direction away from the centre indicated



by circles and arrows in the figure. Starting, say, to the right of the ruled squares with the left edge of the microscopic field just touching the outer boundary line of the squares, count all the white cells to be seen in the field. Then move along to the right till the corpuscles which were on the extreme right of the first field have gone out of sight to the left. Your field is then in the position of the circle marked 2 (Fig. 8). Count all the white cells in this field and so on for four fields. With my objective, four such fields are almost exactly equal to the whole ruled space AAAA. With other objectives of course the number of fields is different.

When we have counted four fields in each of the four directions

indicated by the arrows we have covered as much ground as if we have put four successive drops on the slide after the first one and

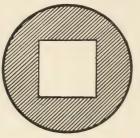


FIG. 9.

counted all the ruled squares in each, and we have saved much time and labor.

(b) Another and better method of attaining this same end is as follows: Cut out of black cardboard a piece of the shape shown in Fig. 9 and of such a size that it will fit into the tube of the eyepiece—the square aperture allowing a space of just one-quarter of a millimetre (one hundred of the ruled squares) to be seen through it with a given objective (say

Leitz No. 5). Four fields as seen through such an aperture can then be counted in various parts of the slide outside the ruled space as explained above.

(c) For any one living where microscopic ruling on glass can be done at a moderate cost, by far the best way is to have the rest

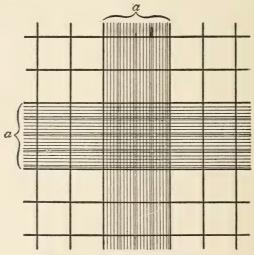


Fig. 10.-Zappert's Counting-chamber.

of the disc A (Fig. 5) ruled off as shown in Fig. 10. Leitz and Zeiss now supply instruments so ruled. I have not been able to hear of any one in America who could do such work at a moderate expense.

- (d) We may work out mathematically what number of squares would be contained on the whole disc were it all ruled like the central portion. This can be done with the aid of a micrometre eyepiece and a mechanical stage. There is some variation in individual instruments, but as a rule the disc outside the central ruled space has an area of about two thousand of the small squares.
- 2. We may use the "white counter" for red corpuscles in the following way: Suck up blood only to the first mark up from the point (i.e., one-fifth of the usual distance) and then Gowers' or Toisson's solution up to the mark 11. This gives a dilution of 1:100, and in anæmic cases, in which the cells are not very numerous, answers well. The same pipette can then be carefully cleansed and used for counting white cells with the acetic acid one-third per cent, and a dilution of 1:10 or 1:20.

Whatever method of counting white corpuscles is adopted, we ought to have at least one hundred corpuscles actually counted to use as the multiplicand of our computation. A single drop from the white counter with a dilution of 1:10 gives us normally about seventy white corpuscles in the four hundred ruled spaces, and by repeating the process with a second drop the result may be made reasonably accurate. This was the method adopted by Rieder' in the immense number of counts made by him.

## II. Durham's Modified Hamocytometer.

In the Edinburgh *Medical Journal* for October, 1897, Herbert E. Durham, of Cambridge, England, describes a self-filling capillary pipette which has considerable advantages over the ordinary Thoma-Zeiss instrument. The account of the device is here given in his own words.

"The apparatus entails no new principle; it is rather to be considered as an adaptation of a number of details, which together seem to present some advantages. As in the Gowers' instrument, there is a separate capillary pipette for measuring the blood, one for measuring the diluting fluid, a mixing vessel, and the counting chamber. A few words may be said about each of these.

"Capillary Pipette.—There is an obvious advantage in the use of a self-measuring pipette. It cannot go wrong by accident. Durham has availed himself of the pipettes introduced by Dr. Oliver, namely, small pieces of thick-walled capillary tube—5 and

<sup>&</sup>lt;sup>1</sup> "Beiträge zur Kenntniss der Leucocytosis," Leipzig, 1892 (Vogel).

10 c.mm. in capacity. These are carefully recalibrated by the makers of Dr. Oliver's instrument—The Tintometer Company.

"There is, moreover, another important advantage attaching to Dr. Oliver's pipette; this consists in the readiness with which it may be cleansed. As he has described, all that is necessary is to pass a piece of darning cotton by means of a needle through the bore of the pipette. All the adherent serum, etc., is completely removed thereby. Durham generally wets the end of the cotton with ether, but this is not absolutely necessary. In passing the needle, it is better to pass it into the pointed end, in case it is not withdrawn perfectly axially, when there is a liability to chip the thinner unsupported glass.

"Any one who has worked much with the Thoma-Zeiss pipette will know how troublesome it is to clean, especially when a number

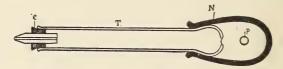


Fig. 11.—Cross-section of Durham's Automatic Blood-Pipette. T, Glass tube (like that of medicine-dropper); N, rubber nipple (like that of medicine-dropper); T, perforation in the nipple; c, cork holder, perforated by capillary pipette.

of observations have to be made in a limited time. Unless it is frequently cleaned out with strong acid, there is a tendency for the deposition of sticky serum remains which interfere with true readings.

"For use, Dr. Oliver's pipettes are mounted by means of a small cork (c) in a large glass tube (T), which is provided with a rubber nipple (N), having a lateral perforation (p) (Fig. 11).

"The mixing vessel consists of a small test tube  $(2\frac{3}{8} \times \frac{7}{16})$  in. for 1 c.c., or  $2\frac{3}{8} \times \frac{3}{8}$  in. for  $\frac{1}{2}$  c.c.). Several such tubes may be kept, so that a number of observations can be made if necessary. For thoroughly mixing the blood and diluting fluid, one or more small glass globules are placed in the tube. By using different colored glass globules, different specimens can be readily differentiated.

"For measuring the diluting fluid, pipettes containing 1 and ½ c.c. are used; these are remarked at 995 and 990 c.mm. and 495 and 490 c.mm. respectively. With these graduations the following dilutions may be obtained: 1:200, 1:100, and 1:50, with the appropriate capillary pipette.

"Having measured the diluting fluid, according to the eventual dilution desired, the blood capillary is filled by touching the exuding drop of blood and allowing it to completely fill itself. The blood may be obtained in the usual manner from the lobule of the ear, the first drops being wiped away.

"The hole in the nipple allows free air-way so that there is no hindrance to the action of capillarity. When filled, any blood on the outside of the pipette is rapidly wiped off, and the tube is inserted into the mixer until the point is one-half to three-fourths of an inch above the level of the contained liquid.

"The nipple is then held in such a way that the hole lies under the thumb of the operator. When this is the case it is slightly squeezed, and then, while the pressure is continued, the bulb is rotated so that the hole is free again. In this way the blood is squirted out, but not sucked back again. The procedure is extremely simple and really requires no practice, given an operator who is not possessed of 'five thumbs.' In order to wash out the remains of the blood the point of the capillary is dropped into the diluting fluid; the bore instantly fills itself. It is then withdrawn and the pressure and rotation of the nipple are repeated. This has to be repeated several times, and occupies a few seconds of time. It has been suggested that a certain amount of error is introduced by measuring the diluting fluid in a pipette, the inner surface of which retains some moisture; this is extremely small in amount if the pipette is emptied slowly, and comparative readings with the Thoma-Zeiss apparatus show that the error is negligible.

"To mix the blood and diluting fluid thoroughly, the mixer is placed between the opposed hands, which are rubbed backward and forward; the mixer is rotated thereby, and the glass globules cause a thorough dispersion of the corpuseles in the fluid.

"A drop of sufficient size is then placed upon the counting chamber, and the cover-slip is slipped on sideways in the usual way. I prefer the Thoma-Zeiss counting chamber.

"The advantages of this method are:

- "1. The ease and thoroughness with which the pipette can be cleaned.
- "2. The manifest advantage of the self-measurement of the blood.
- "3. The avoidance of the objectionable necessity of using the mouth to suck fluids into the pipette.

- "4. The measurement of the diluent can be done carefully and calmly beforehand, and any error corrected without taking any more blood.
  - "5. The greatly smaller cost of the pipette.
- "6. The same pipette is useful for making various dilutions in serum diagnosis, by using several mixing vessels filled beforehand with dilute fluid,"

### CHAPTER III.

OLIVER'S HÆMOCYTOMETER—CENTRIFUGALIZING THE BLOOD

—HÆMOGLOBIN ESTIMATION—SPECIFIC GRAVITY—

STAINED SPECIMENS—BACTERIOLOGICAL

EXAMINATION.

#### OLIVER'S HÆMOCYTOMETER.

RECENTLY a method of estimating corpuscles by means of their optical effect, and without directly counting them, has been introduced by Dr. Oliver. For practical purposes an actual counting of the corpuscles must be considered a necessity; not only since the number of leucocytes is not without importance (e.g., in the diagnosis of enteric fever), but also since these cells may be so abundant that they may interfere with the use of optical methods, as in the case of leukæmia. Nevertheless the instrument is very accurate and useful in many cases. Its principle is based on the fact that if a small quantity of blood is gradually diluted with Hayem's solution in a test tube whose sides are flattened so that its mouth forms a rectangle about 15 mm. by 5 mm., and a candle flame is looked at through the mixture, there is to be seen, when a certain degree of dilution is reached, a bright horizontal line on the glass. This line is made up of a large number of minute images of the flame, produced by the longitudinal striation of the glass. If the quantity and quality of blood used are in every instance the same, the degree of opacity depends wholly on the amount of Hayem's solution added. It is found that with normal blood the amount of diluting solution necessary to allow the image of the candle flame to be seen through the mixture is always the same, and can be very accurately fixed, so that a variation of one per cent in the number of corpuscles can be distinguished by noting the amount of diluting solution which must

<sup>1</sup> Hydrargyri perchloridi	 $0.5~\mathrm{gm}.$
Sodii chloridi	
" sulphatis	 50 "
Aquæ destillatæ	 200.0 c.c.

be added before the image of the flame appears. To collect the blood, Oliver uses a capillary pipette containing about 10 c.mm. (one large drop), and used exactly in the same way as the v. Fleischl capillary pipette (see Fig. 12).

One pipette full of normal blood is gradually diluted in the flattened tube with Hayem's solution until a bright horizontal line

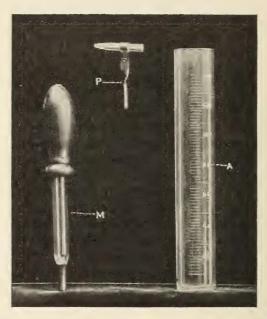


Fig. 12.—Oliver's Hæmocytometer. A, Graduated mixing tube; P, capillary pipette; M, dropper, with rubber nozzle fitting the capillary pipette.

caused by the image of candle flame becomes visible through the mixture. The point to which the column of the mixture then reaches is marked 100, and the space between that point and the bottom of the tube is divided into 100 equal parts. The point marked 100 is then equivalent to 5,000,000 red corpuscles; 90 = 4,500,000, 80 = 4,000,000, and so on, each degree on the scale corresponding to a difference of 50,000 corpuscles (Fig. 12).

# Use of Oliver's Hæmocytometer.

The capillary pipette is first thoroughly cleaned and dried by passing through it a needle and thread saturated with water and then with alcohol and ether. It is then filled in the usual way,

and the outside carefully and quickly wiped if necessary. The medicine dropper (previously filled with Hayem solution) is then connected with the polished blunt end of the pipette by means of the rubber tube (Fig. 12), and blood washed into the test tube. Speed is essential, else coagulation occurs. If the previous hæmoglobin estimation has shown ninety to one hundred per cent of coloring matter, we can safely add the diluting solution rapidly until the

point marked 80 is reached. If the coloring matter is lower we must cease our rapid dilution correspondingly sooner. When we get near the point at which the flame image is likely to appear, the diluting fluid must be added a few drops at a time. After each addition put the thumb over the mouth of the tube and turn it upside down once or twice to mix the blood thoroughly, wiping the thumb each time on the edge of the tube so as to put back what fluid has adhered to it. At a certain point the image will suddenly become visible. It is seen soonest if we rotate the tube on its long axis, as the image becomes visible



Fig. 13.—Showing the Method of Holding Oliver's Hæmocytometer.

earliest at the sides of the tube, but dilution should be continued drop by drop until the horizontal line of light is just visible across the short diameter of the tube. The appearance of the incomplete line at the sides is a constant forerunner of the complete transverse line, and should put one on one's guard as very close watching is needed to recognize it without overstepping the necessary dilution. The opacity remains uniform for many minutes. The whole process should be carried on in a perfectly dark room, and the diffused light of the candle must be shut off from the eye. This is best done by

fitting the tube into the hand as shown in Fig. 13 with the long axis in line with candle, holding the tube *close to the eye*, and standing about ten feet from the candle. In the use of both of his instruments Oliver employs only the small wax candle known as Christmas candles, whose flame is of the most convenient size.

After some experience with this instrument I find it simple, accurate, eye-saving, and rapid. The whole test can be made in five minutes. Its only drawback is the impossibility of making any estimate of the white corpuscles with it. Dr. David D. Scannell made in 1899 a series of observation on patients in my clinic, to test the accuracy of the instrument when compared with actual counts made with the Thoma-Zeiss apparatus. As will be seen by the accompanying table, his results showed that, exclusive of leukæmic cases; the difference in the readings of the two instruments was from 4,000 to 74,000 red cells, an average of 35,000. This implies an error of less than one per cent, granting that the Thoma-Zeiss

No.	Diagnosis.	Thoma-Zeiss red count.	Oliver's hæm reading = red		Remarks.
1	Pernicious anæmia	1.704.000	32 per cent.	1.700,000	
2	Debility (?)	4.368,000	87 "	4.350,000	
3	Normal	4,626,000	92 "	4,600,000	
4	Leukæmia		52 "	2,600,000	Whites, 480,000
5	Pleurisy		95 "	4,750,000	, , , , , , , , , , , , , , , , , , , ,
6	Gastric cancer	2,579,000	51 "	2,550,000	
7	Syphilis		90 "	4,500,000	
8	Secondary anæmia	2,632,000	52 "	2,600,000	
9	Pernicious anæmia	1,178,000	24 "	1,200,000	
10	Lymphæmia	3,726,000	73 "	3,650,000	Whites, 102,400
11	Normal	5,024,000	99 "	[4,950,000]	
12	Pernicious anæmia	2,907,000	59 "	2,950,000	
13	Normal	5,136,000	102 "	5,100,000	
14	Pernicious anæmia	2,934,000	59 "	2,950,000	
15	Debility(?)	4,784,000	96 "	4,800,000	
16	Normal	5,000,000	99 "	4,950,000	
17	Pernicious anæmia	1,596,000	32 "	1,600,000	
18	Debility (?)	4,584,000	92 "	4,600,000	
19	Chlorosis	3,583,000	71 "	3,550,000	
20	Gastric cancer	4,080,000	81 "	4,050,000	
21	Secondary anæmia	4,120,000	82 "	4,100,000	
22	Normal	5,472,000	109 "	[5,450,000]	
23	Gastric cancer	4,120,000	82 "	4,100,000	
24	Debility (?)	4,824,000	96 "	4,800,000	
25	Pernicious anæmia	1,976,000	40 "	2,000,000	•
26	Raynaud's disease	3,486,000	70 "	3,500,000	
27	Chlorosis	4,268,000	85 "	4,250,000	

<sup>&</sup>lt;sup>1</sup> Boston Med. and Surg. Jour., February 15th, 1900.

instrument was exactly correct in each case. In many of these cases I verified Dr. Scannell's readings and counts.

Dr. G. W. Fitz finds that the degree of dilution necessary to make the bright horizontal line appear corresponds with fifty-two corpuscles to every thirty-six squares of the Thoma-Zeiss counter. This means that if a drop of the mixture be placed on the Thoma-Zeiss counting chamber, just after the bright line appears, fifty-two corpuscles are to be found in thirty-six squares. If more or less are found the dilution has been proportionally incorrect.

#### THE HÆMATOCRIT.

The hæmatocrit of Hedin has undergone considerable modification and improvement and as remodelled and improved by Judson Daland has been used to some extent in this country. Its direct and obvious object is simply to ascertain the relative volume or mass of the corpuscles and of the plasma in a drop of blood; but the hope of its advocates has usually been that it would supplant entirely or mostly the long, tedious, and eye-destroying process of counting with the Thoma-Zeiss instrument.

To use the Daland hæmatocrit we prick the ear as usual and with the help of a bit of rubber tube attached to one end of the capillary tube (Fig. 14) suck in enough blood to fill it entirely.

As soon as it is full, put the finger (greased with vaseline) tightly over the free end of the glass tube and then, but not till then, draw off the rubber tube and adjust the glass as quickly as possible in the place prepared for it on one of the horizontal arms of the whirling machine (Fig. 14). A similar tube (empty) should be put on the other arm of the crosspiece to make the balance true. The handle of the instrument is then revolved at least seventy times a minute for two minutes, at the end of which time (sometimes less) the column of blood cells is packed so tight that no further whirling has any effect on its length.

To estimate the number of red corpuscles from the length of the column, we call each degree of the scale on the tube 100,000 cells, or a little more. Thus if the blood column in the tube ends at about the mark 50, we consider that the blood has rather more than 5,000,000 red corpuscles per cubic millimetre. So far all observers agree on the figures, but as to just how much more or less than 100,000 each degree on the scale is worth there is some variation

between different observers. Daland i finds that the degree of the scale on the capillary tube corresponds to 99,390 corpuscles.

So far as I can learn, the use of this instrument in Europe has been chiefly for the direct information it affords as to the *volume* of

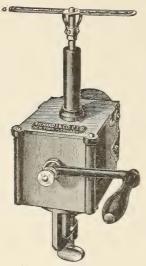


FIG. 14.—Daland's Hæmatocrit. Two capillary tubes in place on the horizontal whirling beam. The instrument is to be fastened to the edge of some solid and bulky piece of furniture by means of the thumbscrew seen at the bottom of the cut. If not very tightly secured, it will work loose when the handle is revolved rapidly.

the red cells and the amount of respiratory surface in the blood, rather than for the indirect information it may give us as to the *number* of the red cells. It does not seem as yet to be supplanting the Thoma-Zeiss counter.

Its bulk and the noise it makes must for the present, I think, prevent its extensive use outside of hospitals. The noise it makes is a very loud and disagreeable one, and will deter many from using it in private practice.

#### HEMOGLOBIN ESTIMATION.

- 1. Tallqvist's Hæmoglobinometer.
- 2. Dare's "
- 3. Oliver's
- 4. v. Fleischl's

Until recently the instrument most used both here and in Europe was that of v. Fleischl. In France Hayem rules supreme in the matter of instruments, as in everything else concerning the

blood, and in England Oliver's apparatus is used to a certain extent. Within a year, however, a contrivance originated by Tall-qvist<sup>2</sup> has come into use and deserves, in my judgment, to supplant all others in clinical work. I shall therefore describe it first.

## I. Tallqvist's Hæmoglobinometer.

A drop of undiluted blood is soaked into a bit of filter paper of standard quality and compared (by ordinary reflected daylight) with a paper color-scale of ten tints, ranging from ten per cent to

<sup>&</sup>lt;sup>1</sup> University Med. Mag., November, 1891.

<sup>&</sup>lt;sup>2</sup> Tallqvist, St. Paul Med. Jour., May, 1900.

one hundred per cent. The scale was prepared by imitating in water color the tint of the blood of anæmic patients (using the v. Fleischl instrument) when soaked into the standard filter paper. The water-color standard colors were then reproduced in lithograph, and the lithographed scale bound up with fifty sheets of the standard filter paper makes an apparatus which can be easily slipped into the pocket and carried to the bedside.

In making the comparison the blood stain is put against a background of white filter paper beside the color scale, and moved along until a match is found. The comparison should be made as soon as the stain has lost its humid gloss, and before it is thoroughly dry. Artificial light cannot be used. Errors of ten per cent are possible, but it is my belief that far greater errors than this are frequently made with v. Fleischl's or Oliver's instrument in the hands of the great majority of physicians. Tallqvist's scale costs but \$1.25, and can be used by any one with sufficient accuracy for practical purposes, and with a celerity that makes hæmoglobin estimation no more of an undertaking than feeling the pulse. I have used the instrument in several hundred cases, and have never yet been misled by it, nor found a greater error than ten per cent in comparison with Oliver's instrument.

## II. Dare's 1 Hæmoglobinometer.

This excellent instrument is undoubtedly more accurate than Tallqvist's, and would be preferable to all others but for its cost (\$20), its bulk, and the time necessary to make an observation and to clean the parts.

As in Tallqvist's method, undiluted blood is used, and this constitutes an advantage over both v. Fleischl's and Oliver's instruments. The blood is drawn by capillary attraction into the slit between two slabs of glass, one transparent, the other translucent and white, so as to diffuse the light used for illumination.

The color of the blood is then compared with different portions of a circular disc of colored glass revolved by means of a thumb screw so that different tints are successively brought side by side with the blood tint. Transmitted light from a candle is used for illumination, and the observation is made through a telescoping camera tube excuding all extraneous light. As we turn the screw and bring different tints of the glass standard into comparison with

the layer of undiluted blood, the percentage of hæmoglobin can be read off from the etched scale which appears at a point opposite the color apperture. The sharply bevelled edge of the opening rests directly over the reading indicated. A pivoted black screen protects the observer's eyes from the direct light of the candle, and may occasionally be brought over the color apertures so as to rest the eye.

The instrument is so made that blood film and standard color disc are viewed side by side in a horizontal plane through two circular holes 5 mm. in diameter which are considerably magnified by a lens in the telescoping camera tube.

In using the instrument we need no dark room—a great advantage. The instrument is simply pointed at some dark surface—a dark coat or corner. In order that the blood and the color disc should be equally lighted, it is essential to see that any curve that exists in the candle wick should point straight toward or away from the centre of the instrument in line with the juncture of the springs which support the candle.

The reading should be completed before the blood film begins to shrink in from the edges, i.e., within ten minutes.

The advantages of Dare's instrument are:

- 1. Its accuracy; using undiluted blood and making allowance as it does for the color curve, it is, I believe, more accurate than any other clinically available instrument.
- 2. Leucocytosis does not disturb the reading (as it does in v. Fleischl's instrument).
- 3. The errors and waste of time incident upon dilution are avoided since the instrument uses undiluted blood.
  - 4. No dark room is needed.
- 5. It can be used and cleansed much more quickly than any other instrument except Tallqvist's.

My reason for preferring Tallqvist's instrument despite these merits of Dare's are:

- 1. Because accuracy greater than that obtainable with Tallqvist's instrument, is seldom practically important.
- 2. Because an observation can be made with Tallqvist's hæmo-globinometer in about one one-tenth of the time needed for using any other instrument, *i.e.*, in about twenty-five seconds.
- 3. Because the Tallqvist instrument takes so little room and needs no cleaning or preparing for use.
  - 4. Because it is so cheap.

### III. Oliver's Hæmoglobinometer.

Oliver's instrument corrects two errors which are inherent in v. Fleischl's.

- 1. It has no sliding scale of color, but compares the blood tint successively with definite tints of glass, each of which is even. The tints are worked out to correspond to the specific dilution curve of blood, for:
- 2. Since every colored liquid changes color at a different rate when diluted, the dilution curve of blood does not correspond to that of glass (which behaves in this respect like a liquid). The glass wedge of v. Fleischl's instrument represents a single color regularly diluted and does not correspond in its degrees to the colors of blood diluted at a similar rate. The scale of Dr. Oliver's instrument is measured to correspond to the actual colors of the blood's dilution curve, by means of the tintometer.

In other respects the principle of the instrument is like v. Fleischl's, and the method of using the two is practically the same except that in Oliver's reflected light is used instead of transmitted light. Oliver's instrument consists of a series of twelve tinted glass discs corresponding to the hæmoglobin percentages from 10 to 120 and arranged in two rows (see Fig. 15, a). The intermediate degrees are measured by means of "riders" of colored glass, which can be laid on top of the primary color discs so as to deepen the tint seen.

The capillary pipette (Fig. 15, b) is somewhat stouter than v. Fleischl's, but is used in the same way to collect the blood, which is then forced out of it with water from a medicine dropper (which is fitted with a rubber tube to slip over the blunt end of the pipette) (Fig. 15, c) and washed into a mixing cell (Fig. 15, d) similar to v. Fleischl's, except for the absence of a central partition. Here the blood is mixed in the usual way with water and the cell filled to the brim and covered with a small glass plate; a bubble always forms, but by turning the cell or moving the cover-glass we can usually get the troublesome shadow thrown by the bubble out of the color field. The blood thus prepared is brought close to the scale and there compared with the tint of the different standard color discs. If it matches one of them the observation is complete; if not we use one of the glass riders which enables us to read within two and a half degrees. A fuller set of riders

can be obtained so as to make it possible to read down to one per cent.

The standard is usually arranged for candle-light, but another set of discs can be obtained adjusted to daylight readings. The latter are less accurate. The same precautions as to the exclusion of outer light by means of a "hydroscope" tube, resting the eye frequently, etc., must be observed with this instrument as with v. Fleischl's. [It can be obtained of J. H. Smith & Cie., Zurich



Fig. 15.—Oliver's Hæmoglobinometer. a, Standard color discs; b, capillary pipette; c, washing tube; d, mixing cell.

(Wollishoften), for 115 francs plus duties and expressage, or of the Tintometer Company, 6 Farringdon Avenue, London, E. C.] The candle should be placed three or four inches from the instrument and arranged to light both the blood and the color discs alike.

A word as to the use of the riders. The instrument as used for clinical work usually has two riders: the one having the deeper tint is used on the upper half of the scale, the other on the lower. Suppose we have decided that the blood color is between 60 and 70. Put the rider on the 60 disc and compare again. If the blood is darker than the 60 disc plus the rider, the percentage is approximately  $67\frac{1}{2}$  (since it is higher than 60 + 5 [the rider] and lower

than 70). If it just matches the 60 plus its rider, the reading is 65. If the blood is paler than this, yet darker than 60, it is about  $62\frac{1}{2}$ . An error of about 2 degrees is obviously inevitable.

### IV. Use of v. Fleischl's Hæmometer.

(a) Fill on one side of the metallic cell (a, Fig. 17) about one-quarter full of distilled water. Put the end of the little pipette (B) horizontally into the side of the blood drop, which will at once fill

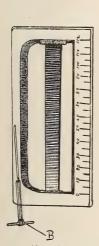


Fig. 16.—A, Colored glass; B, capillary pipette.

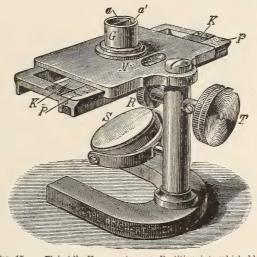


FIG. 17.—v. Fleischl's Hæmometer. a, Partition into which blood is put; a', partition into which water is put; G, mixing cell; K, K, colored glass slip (see Fig. 16, A); P, P, metal frame on which scale is marked; R, S, reflector; T, screw which moves the frame, P, P.

the tube by capillary attraction. Quickly wipe away any blood that may be on the outside of the pipette. Then put it into the water contained in one of the partitions of the metallic cell and rattle it quickly back and forth, so that the water may be forced in first at one end and then at the other.

(b) After this the expulsion of the blood may be completed by forcing water from a medicine dropper through the capillary pipette and into the compartment where the mixing has been begun. Using the metal handle of the pipette, mix the blood and water in every part of the compartment. Then fill both compartments of the cell to the brim with distilled water, and adjust the compartment con-

taining the clear water so that it comes over the slip of colored glass, while through the compartment containing the blood light thrown upward by the reflector below passes directly to the eye. Turn the thumb screw (see Fig. 17, T) back and forth until the color of the glass is the same as that of the blood, and read off the

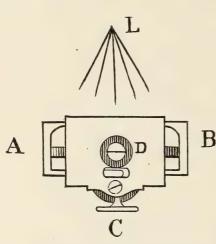


Fig. 18.—L, Light; A and B, right positions for observer; C, wrong position for observer; D, cell in place.

number on the scale which corresponds to that color. This gives the percentage of hæmoglobin, 100 being the color of normal blood for men and 80-90 for women.

- (c) Matching the colors is not at all easy at best, but may be somewhat aided by observing the following precautions:
  - 1. Do not stand (or sit) facing the light, but sideways (i.e., at A or B, never at C, Fig. 18). By sitting as in Fig. 18, A or B, we get the compartments whose colors we are to match, on the right

and left halves of the retina, which are equally sensitive in most persons.

- 2. Use as little light as possible, and always less light for a blood having a low hæmoglobin percentage than for one nearer the normal.
- 3. Roll up a piece of paper (preferably black) into a tube of such size that it will fit over the metallic cell (D, Fig. 18), and rest on the platform of the instrument. Looking through this with one eye we can judge the color more accurately.
- 4. Use first one eye and then the other, and never look more than a few seconds at a time.
- 5. Move the thumb screw with short, quick turns rather than slowly and gradually, for sudden color changes affect the retina more than gradual ones.
- 6. If the preliminary reading shows one of thirty per cent or less, two or three pipettes full of blood should be used and the reading divided by 2 or 3. A considerable error can thus be avoided.

### Necessary Errors.

A considerable error is absolutely necessary, inasmuch as the bit of colored glass to be seen at any one time through the aperture of

the instrument is not (like the blood) all of one tint, but includes a variation of twenty per cent in color, i.e., if the glass appearing at one end of the aperture is opposite 50 on the scale, that seen at the other end of the aperture will either be at 30 or at 70. This difficulty is somewhat lessened by shutting off from view all but a small section of both compartments with a bit of black cardboard or metal in which a slit is cut as in Fig. 19. The slit is put at right angles to the partition which divides the cell so that the blood tint is seen at b and the glass tint at w.



Fig. 19.—Shield for Use with v. Fleischl's Hæmometer.

Many persons are not sensitive enough to

colors to attain any reasonable degree of accuracy with the instrument, and there is moreover a very considerable difference between different instruments in respect to the color of the glass slip.<sup>1</sup>

All these difficulties render the instrument an unsatisfactory one in many ways. Its bulk and expense are also considerable and in my opinion its use should be entirely abandoned in favor of Tallqvist's or Dare's instrument.

### ESTIMATING THE SPECIFIC GRAVITY OF THE BLOOD.

The simplest and most available method for clinical use is that of Hammerschlag, a modification of Roy's method. Chloroform is heavier than blood; benzol is lighter. Mix in a urinometer glass such quantities of the two that the specific gravity taken by an ordinary urinometer is about 1059, i.e., that of normal blood. Puncture the ear, draw a drop of blood into the tube of a Thoma-Zeiss pipette, a small medicine dropper, or any other capillary tube, and blow it out again into the chloroform-benzol mixture. The blood does not mix at all with these liquids but floats like a red bead. If

<sup>&</sup>lt;sup>1</sup> Old instruments read lower than those recently manufactured.

<sup>&</sup>lt;sup>2</sup> Wien. klin. Wochenschrift, iii., 1018, 1890.

<sup>&</sup>lt;sup>3</sup> Proceedings of Physiological Society, 1884.

it sinks to the bottom add chloroform, if it rises to the top add benzol, until finally the drop remains stationary in the body of the liquid, showing that its specific gravity is just that of the surrounding mixture. Then take the specific gravity of the liquid, as we do of urine, and you have the specific gravity of the drop that floated in it. The following precautions are needed:

- 1. Have the inside of the urinometer glass perfectly dry and clean; otherwise the drop of blood may cling to it and flatten out against it.
- 2. It is usually well to have more than one drop of blood in the glass in case any mishap occurs with the first one.
- 3. Add the chloroform and benzol a few drops at a time, and after each addition stir the whole mixture thoroughly with a glass rod.
- 4. If we have reason to suppose the blood will be lighter than normal (i.e., if the hæmoglobin is probably low, vide supra), it saves time to start with a lighter mixture of chloroform and benzol.
- 5. Avoid having any air within the blood drop. This can generally be seen either in the capillary tube or after the drop is in the mixture. It is safer to take the middle portion of the blood drawn into the capillary tube, as both the first and the last portions of the column are more apt to have air in them.
- 6. The whole process should be done as quickly as possible, else the chloroform or benzol may evaporate or work into the blood drop and so affect its weight.

It is better to have a urinometer with a scale running as high as 1070, but this is not essential, for the clinically important specific gravities are *low*, not high.

The importance of the specific gravity of the blood, as hinted above, is not so much for itself, but because it runs parallel to the percentage of hæmoglobin and gives a figure from which the latter can be computed.

The specific gravity of the blood plasma varies very little (except in *dropsy* from any cause), and in the corpuscles themselves the variable element is the hæmoglobin. Consequently in most non-dropsical patients the specific gravity of the whole blood varies directly as the hæmoglobin. The following exceptions to this rule must be borne in mind.

<sup>&</sup>lt;sup>1</sup>Except in dropsy in which the corpuscles themselves may get water-soaked.

- 1. In leukæmia the specific gravity is relatively higher than the hæmoglobin on account of the weight of the leucocytes.
- 2. In pernicious anæmia with high color index (see blow) the hæmoglobin is about two per cent higher than we should gauge it to be judging by the specific gravity.

To estimate the percentage of hæmoglobin from the specific gravity, one of the following tables may be used, modified from Schmaltz, "Pathologie des Blutes," etc., Leipsic, 1896, using a direct weighing method. Apparently a degree of specific gravity means much more at the top of the scale (i.e., 6.6 per cent) than at the bottom ( $1\frac{2}{3}$  per cent). This table has been verified by the research of Yarrow (University Med. Mag., 1899) through comparison with a standard solution of 13.77 gm. of prepared hæmoglobin in normal salt solution (up to 100 gm.). It appears to be very accurate.

Spec. Grav.		Hæmo	globin.		Spec. Grav		Hæmo	globin.	
1030	=	20 per	cent.	±	1049	=	60 per	cent.	士
1035	=	30	66	66	1051	=	65	44	66
1038	=	35	44	66	1052	=	70	66	66
1041	=	40	66	66	1053.5	=	75	44	66
1042.5	=	45	66	44	1056	=	80	44	66
1045.5	=	50	66	66	1057.5	=	90	44	66
1048	=	55	"	66	1059	=	100	44	66

### STUDY OF THE FINER STRUCTURES OF THE BLOOD.

The study of dried and stained specimens with the help of the aniline dyes gives us much of interest and importance in regard to the blood. More can be told about a given case by the study of a dried and stained cover-glass specimen than by any other single method.

## Preparation of Cover-Glass Specimens.

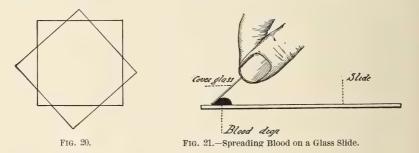
(a) Covers carefully cleaned and polished are arranged at the bedside in such position that we can quickly pick them up without touching their surfaces (see Fig. 1). The ear is punctured in the usual way, and one of the cover-glasses touched to the summit of the drop as soon as it emerges. This cover-glass is then let fall

<sup>1</sup>I often poise them on corks so that their corners are readily accessible to the fingers. The process of making blood films is far easier if another person prepares the drop for us so that we can stand ready with a cover-glass in each hand to catch the drop as soon as it emerges.

upon another in such a way that their corners do not coincide (Fig. 20). If the covers are clean the drop spreads at once over their whole surface; as soon as it stops spreading, slide off the top one without lifting them apart, but exactly in the plane of their surfaces. Have a gas or alcohol flame at hand and dry instantly if you want to get the very best specimens; but this is not at all necessary for most clinical purposes. The under cover-glass is always better spread than the upper.

The above method needs a good deal of practice. (b) An easier way of preparing blood films is as follows:

Put a moderate sized drop of blood on a glass *slide* (not a coverglass) near one end. Hold another slide (or a cover-glass) against



the first in the position shown in Fig. 21. Move the slide along in the direction shown by the arrow so as to spread the blood drop over the whole length of the glass as thinly as possible. The quicker the whole process is performed the better will be the results. After drying the film in the air it can be fixed and stained as below described

(e) Howard and Pakes' use the following modification of Manson's method: Blood is collected on a bit of paper and with this is spread along the surface of a slide or of a large  $(1\frac{1}{2}$  in. by  $\frac{3}{4}$  in.) cover-glass.

"We have tried various kinds of tissue paper and have finally accepted cigarette paper as the most convenient. There are two small points to be noticed. Firstly, the edge used must be the original machine-cut edge; and secondly, it must be that which is parallel to the ribs. The best papers are the Tarlene, or the Zigzag, not the familiar A. G. papers. Strips are cut across the ribs so that each is about half an inch wide and as long as the original

<sup>1</sup> Journal of Tropical Medicine, February, 1899.

cigarette paper is wide. Should cigarette papers not be at hand, ordinary note paper may be used, but it is not nearly so good.

"In making the film the strip is held between the thumb and first finger and is lowered till the under surface adjacent to the machinecut edge just touches the drop of blood as it rests on the skin, and then by a slight lateral movement the drop is converted into a streak,



FIG. 22.

as in the diagram. This end of the strip is at once laid blood downward on one end of the cover-slip, the other end being still held, and the blood having been allowed to spread out between the paper and the cover-slip, the paper is slowly drawn along the slip toward the other end. A fresh strip of paper should be used for each film "

## Fixing the Films.

These films have now to be fixed, either by heat or by half an hour's immersion in absolute alcohol and ether (equal parts), or by the same mixture (30 c.c. each) plus five drops of a saturated alcoholic solution of corrosive sublimate (five minutes' immersion), by chromic acid two per cent, or by exposure to the vapor of forty-five per cent formaldehyde. I have used all these methods, but found none of them to compare favorably with the method of heat fixation when we wish to study the leucocytes or the nuclei of any cell.

When we wish to see chiefly the changes in the red cells (as in studying the malarial organism, nucleated red corpuscles, degenerative changes, etc.), the alcohol-and-ether method is good. But when, as in the majority of cases, it is the white cells in which our interest centres, the use of heat is very greatly to be preferred. Heat serves not simply to fix the cells on the glass and to prevent degenerative changes, but also to modify and greatly improve the staining power of the cell when Ehrlich's triacid stain is used.

The method of fixation by alcohol and ether needs little comment, the cover-glasses being simply left in the mixture half an hour or as much longer as is convenient. Half an hour is enough,

In most cases we use dry heat. The best way to do this is in a dry-heat sterilizer at a temperature of 115°-155° C., according to the size and construction of the oven and the kind of stain used. The temperature must be watched very closely, and as soon as it reaches the desired point the heat should be removed. Gradual heating and gradual cooling are best. If we cannot easily get access to such an instrument, we can manage very well with any small iron or copper box having a door or lid and a hole for a cork which is perforated for the thermometer bulb. This supported over a gas or alcohol flame does very well. It needs about five minutes to get the temperature to 150° C., and as soon as it gets there the specimens should be taken out. The thermometer bulb must rest as near as possible to the blood films without actually touching them. Ovens vary a good deal in the amount of heat actually conveyed to the film with a given reading on the thermometer. Some heat the film as much with a reading of 115° C. as others with one of 150° C. The proper temperature must be ascertained once for all by experiment with each oven. The same end can be accomplished somewhat less accurately with a strip of copper supported over a Bunsen burner or a small gas or oil stove. The copper plate should be about a foot long and two or three inches wide. Such a plate supported on an iron tripod over a flame gets, after a few minutes, to have a fixed temperature at any given distance from the flame, the heat passing off at the end of the plate as fast as it comes, and so not accumulating. On this plate find the boiling point of water by dropping small drops of water on it, and put the cover-glasses at this point face downward. They may be left there for from fifteen minutes to as long as you please; but with the stain which I have used, fifteen minutes' heating gives as good results as a longer period, and excellent specimens can often be made with five minutes' heating. After allowing the specimens to cool they are ready for staining. A very fair oven can be made out of a five-ounce quinine can, by

¹ With a little practice one can learn to make excellent specimens by simply passing the cover-glass through a Bunsen or alcohol flame about twenty times very rapidly. The rate of speed must be learned by experiment, *i.e.*, such a speed and such a number of exposures to the flame as turns out to give on staining a bright yellow color to the red corpuscles (never red or brown or gray), a good definition to the blue stained nuclei and to the violet or pink granules of the polynuclear leucocytes. These are the essentials of a well-stained specimen, and they depend (a) on the heating, (b) on the make of stain, but only slightly on the length of staining (vide infra).

boring small holes in opposite sides and drawing through them copper wires on which to support a piece of wire netting to serve as a shelf for the blood films. A circular hole punched in the top of the can admits a perforated cork through which a thermometer registering 200° C. is passed. The whole is heated by a Bunsen burner.

#### STAINING.

For all details of structure the Ehrlich tricolor mixture or one of the numerous modifications of it is most convenient. The most useful and easily obtained of these is made by mixing:

Saturated watery solution of orange G.................. 6 c.c.

	46		"	66	66-	acid fuchsin 4 "
$T_0$	these	add	a few	drops	at	a time, shaking between each addition
	Satura	ated '	watery	solution	n of	f methyl green 6.6 c.c.
eT11		1				

Then add:

Glycerin	5 c.c.
Absolute alcohol	10 "
Water	15 "

Shake well for one to two minutes. Let stand twenty-four hours. Do not filter. G. Grubler's colors are best.

I have used only this stain for the past six years, and have never seen any other which compares with it in brilliancy and general usefulness.

The staining process is remarkably simple. A drop of the stain is simply spread over the surface of the cover-glass specimen with a glass rod and washed off again with water after five minutes or as much longer as is convenient. With this mixture it is impossible to overstain. If the specimen look too dark (brown or red instead of orange-yellow) it is not because of overstaining, but because of underheating. It needs a good deal of heat to bring out the full brilliancy of the three colors, and the 100°–120° C. usually recommended for heating is entirely insufficient with this stain unless continued for a long time.

If overheated the specimen looks pale lemon yellow to the naked eye, and under the microscope everything is blurred and dim. Dr.

<sup>1</sup> An absolutely reliable triple stain from Ehrlich's latest formula can be had of Walter Dodd, apothecary to the Massachusetts General Hospital. A 65-cent bottle will stain several thousand specimens.

H. F. Hewes has suggested the following method of improving the definition of the nuclei. After washing off the triple stain he pours upon the film a saturated aqueous solution of methylene blue and after a second or two (not more) washes it off again. The specimen is then dried in blotting paper and mounted in balsam.

I am convinced that any one who has once seen how much is brought out by a good make of triple stain followed by methylene blue for a second or two will never use any other for clinical purposes. The blue counterstain also brings out clearly the outlines of the malarial parasite against the yellow of the red corpuscle. Eosin (one-per-cent alcoholic solution) followed after a few minutes by Delafield's hæmatoxylon for one minute, or methyl blue one-half minute, gives a very striking contrast stain, but does not bring out the points most essential in clinical blood work. To "control" Ehrlich's triple stain with eosin-hæmatoxylon or eosin-methyl blue is like controlling a chronometer with a fifty-cent clock. The latter stains are very valuable for the study of the finer structure of nuclei, for karyokinetic figures and basophilic granules, but not for diagnosis.

After staining and washing in water, the covers are dried between layers of filter paper and mounted in Canada balsam, ready for examination with the one-twelfth oil-immersion lens, with wide-open diaphragm.

## Differential Counting.

The only procedure in the microscopic examination of such specimens which needs any description is that of making the so-called "differential count" of the leucocytes (i.e., determining what percentage of the leucocytes present belongs to each of the sub-varieties as described on pp. 62–67). To do this accurately we should examine at least five hundred leucocytes—the examination being simply the classification of them under their different sub-varieties. A movable stage is very convenient though not essential for this purpose. With such a stage the technique is simply to start with the lens in, say, the upper left-hand corner of the blood film and, by

<sup>1</sup> Of late I have used dry lenses a great deal—the 7 or even the 5 of Leitz—on account of their larger field. Most cells can be easily recognized with this power after we have well learned their looks by earlier study of specimens with the immersion lens. If in doubt about any cell, it is easy to pull out the tube of the microscope or put on the immersion lens.

turning the screw of the mechanical stage, move the preparation slowly past the eye until the upper right-hand corner is reached. During this process as the cells appear in the field they are checked off and put down under one or another heading. Then move the stage so that the lens is just one field's diameter nearer the right hand lower corner of the preparation, and go back again from right to left, following the serpentine track indicated above in Fig. 7. To move the lens just one field's diameter we have only to fix the eye on a cell at the extreme edge of the field, and then move the stage till that cell disappears out of sight on the opposite side of the field. Thus we avoid any chance of counting the same cells twice, and yet are sure not to miss seeing any.

As we go back and forth in this way, we notice chiefly the white cells of course, but yet keep our eyes open for any unusual appearances in the red cells. Usually these move by in a monotonous stream, one looking much like another, but in pathological blood we must always be on the lookout for nucleated red cells, degenerative changes, and variations in size and shape. In malarial cases of course our scrutiny is directed chiefly upon the *red* cells.

If we have not the help of a movable stage we try to do the same thing moving the slide with the fingers. With moderate care there is no danger of counting the same cells twice, but we cannot help missing a good many altogether, so that although accurate the process takes longer.

When leucocytosis is present, at least one thousand leucocytes can be found in a single well-spread seven-eighth-inch cover-glass specimen. In normal blood we may need to go through two or three covers.

#### BACTERIOLOGICAL EXAMINATION.

Blood obtained by the ordinary method of puncture is not fit for bacteriological examination. The following is the better way:

Sterilize the skin over the flexor surface of the bend of the elbow, and wash off thoroughly the agents used for sterilization with boiled water or boiled normal salt solution. Have an assistant grasp the upper arm so as to prevent the venous return and distend the large veins at the elbow. Into the most prominent of these plunge a sterilized hollow needle connected with the bulb of a sterilized <sup>1</sup> See Kühnau's comparative experiments in Deut. med. Woch., 1897, No. 25

syringe. All traces of antiseptics must be carefully washed out of the needle and the syringe bulb before using.

When the needle penetrates the wall of the vein the blood usually begins to flow into the bulb of the syringe, and this is hastened by gently withdrawing the piston until 1-2 c.c. of blood are in the bulb. Then withdraw the needle, press a pad of sterilized gauze over the wound, and expel the blood before it coagulates into a blood-serum culture tube so that it shall run down over the whole surface of the "slant" and collect a little at the bottom. The tubes are then put at once into the thermostat.

In examining for the gonococcus the blood is to be mixed with equal parts of agar-agar (previously melted down so as to be mixable but not hot enough to kill the organisms), and then plated.

The further examination of cultures falls outside the scope of this book.

In the above procedure the only difficulties are: 1. Sometimes it is hard to find a vein and to get the needle into it. 2. Occasionally we get the needle entirely through the vessel into the tissues on the other side.

If the blood does not flow readily into the bulb one of these two mistakes is usually the cause, but occasionally in those whose vessels are very small or whose circulation is very feeble (as in the moribund) it is very hard to get the requisite amount of blood. Only practice helps us to avoid these difficulties.

The procedure causes hardly more pain than the use of an ordinary subcutaneous injection; the process of sterilization is usually more irksome to the patient than the puncture.

Bleeding is trifling, and within twenty-four hours there is usually no trace of the puncture left. A sterilized dressing with moderate pressure should be applied.

Estimation of the Time and of the Completeness of Coagulation.

In certain conditions, particularly in acute exanthemata, clotting is slow or fails to occur. This is still more marked in the various forms of the hæmorrhagic diathesis. In obstruction in the biliary tract with or without jaundice, clotting may be greatly delayed, and this fact is of great importance to the surgeon with reference to the question of operation.

Hayem has called attention to the fact that in purpura hæmorrhagica the blood clot may form, but fail completely to retract. He further believes that the blood of pernicious anæmia may be distinguished from specimens obtained in cases of secondary anæmia by the fact that in pernicious anæmia there is an incomplete formation of serum.

In both these conditions the blood plates are greatly diminished. He has found similar changes in some other cachectic conditions.

The importance of these facts in the prognosis of purpura may be considerable—the severer forms being thus distinguishable from the milder types (according to Hayem) even during the remissions or non-hæmorrhagic stages of the disease.

For the estimation of coagulation time the simple little instrument devised by Wright is sufficient. This consists simply of a set of from six to twelve capillary tubes of about the same calibre (.01 to .0125 inch) into each of which a blood column about two inches long is aspirated. The tubes are then set perpendicularly in a rack and at regular intervals the condition of the blood is tested by blowing into one of the tubes. When coagulation occurs, the tubes are found to be blocked with clot.

Normally coagulation occurs in these tubes in about three minutes. In disease, especially in cases with biliary obstruction, coagulation may not occur until ten to fifteen minutes have elapsed.

#### OTHER METHODS OF BLOOD EXAMINATION.

It is perhaps worth while briefly to mention some other methods of blood examination of which no account will be given.

- 1. Determination of the alkalinity of the blood. No accurate and clinically available method has yet been devised. Despite the interesting work of Kraus, Caro, Löwy, Biernacki, v. Limbeck, and others, I am still unable to get hold of any clinically valuable information given by the determination of alkalinity.
- 2. Resistance of the red corpuscles to the influence of distilled water. As is well known, water breaks up red cells, but if we add a certain amount of alkali, say NaCl, the cells remain uninjured. The amount of NaCl which has to be added to prevent the destruction of red cells is from 0.44 to 0.48 per cent. Under certain pathological conditions it needs either more or less of the salt to keep the cells intact, i.e., they possess an increased or diminished power of resistance against the destroying influences of distilled water. The degree of concentration necessary to maintain red corpuscles intact

is known as the *isotonic coëfficient* of the blood as stated in terms of a given salt; 0.44-0.48 is thus the coefficient of normal blood corpuscles in NaCl.

The resistance of the blood cells to the influence of electricity, heat, and mechanical pressure has also been investigated in various conditions of health and disease. Welch has suggested a possible clinical application of these facts. There is much, he says, for the view that the number of blood plates is an index of lowered resistance in the red cells. When resistance is lowered and blood plates increase, intravascular thrombosis—so much dreaded in chlorosis, so eagerly desired in aneurisms, is more apt to occur.

3. The amount of solids in a given quantity of blood can be determined by weighing a given amount of blood before and after six hours' drying at 65° C. Inasmuch as the hæmoglobin percentage and the specific gravity run practically parallel with the amount of solids this method has no considerable clinical value.

# PART II.

### PHYSIOLOGY OF THE BLOOD.

#### CHAPTER IV.

Only such portions of our knowledge of blood physiology will be entered upon here as are necessary for an understanding of the small group of pathological changes which can be profitably investigated by clinicians. This limits us for the present to the morphology of the blood, its coloring matter, and its density under physiological conditions.

#### APPEARANCE OF FRESH NORMAL BLOOD.

A drop of normal blood spread between slide and cover-glass as directed on page 9 and examined immediately with a one-twelfth immersion lens, amazes us first of all by the entire absence of any red color. All we see is a colorless liquid in which masses of very pale greenish-yellow discs are floating or lying.

# I. Red Corpuscles.

- (a) If the blood is spread thickly the blood discs are often arranged in the form of rouleaux (Fig. 23). The entire absence of this tendency to rouleaux formation is pathological. It is to be avoided, of course, as far as possible, as it gives us only the thin edges of the corpuscles to look at, and covers up much that we need to study. Thin spreading of the blood is therefore important.
- (b) There is not much variation from the accurately round shape of each corpuscle in normal blood, except where one is indented by another. As they are moved about by the currents set in motion by the gradual drying up of the plasma and strike against each other, they bend, double up, or indent each other, like bags of jelly, but yet always have a strong tendency to return elastically to their round outline when free from pressure. Thus a corpuscle passing through a narrow passage between two leucocytes will be flattened

out like a worm; but as soon as it emerges on the other side, it will be as round as before.

- (c) The central biconcavity of the cell, being thinner than the rim, is lighter colored. Just how much lighter should be learned by practice so that we may detect any abnormal pallor of the corpuscles due to lack of hæmoglobin. Pallor is to be seen mostly in the centre of the cell, which in extreme cases seems almost transparent. This is not to be confounded with the highly refractile, glistening-white centres seen as a mark of necrosis as soon as the blood begins to dry up. A fuller description of these appearances is given in the chapter on the malarial organisms, with some forms of which they may be confounded.
- (d) Slight *variations in size* are present among normal red discs, and here again only practice can teach us where the normal limits end and the pathological begin. Cells may be (pathologically) *all* undersized or *all* oversized, so that a standard of comparison is not always to be looked for in the preparation itself.
- (e) If we focus carefully on a single red cell, we can usually make out a fine, wavy, so-called *molecular motion* in it. This is quite different from the active amœboid movements observed in dying cells, and from the rapid dancing of malarial pigment.
- (f) The familiar appearance of spines all over the cells usually called "crenation" need not be described here (see Fig. 26, p. 84).

But it is the very earliest beginning of crenation that leads to mistakes, as when only one projection has been developed and that points toward the eye, so that a bright spot in the corpuscle is all we see.

- (g) Unless we disinfect the skin before puncturing we must be prepared to find in fresh preparations (a) oil drops; (b) epithelium; (c) particles of "dirt"; (d) small colorless motile organisms about  $1 \mu$  in diameter (Müller's "Haemoconien"—see p. 60).
- (h) We may make a rough estimate of the number of red cells present if we take care to spread the drop of the same thickness each time. The eye gets used to the ordinary look of a well-filled field of corpuscles and notices a look of thinness if any considerable anæmia is present.
- (i) The degenerative changes to be seen in normal blood after long exposure to the air, which can get in between slide and cover,

<sup>&</sup>lt;sup>1</sup> In some conditions the blood really contains fat (ride infra, "Lipæmia").

are described in detail later on. In pathological blood we may find these as soon as the blood is drawn.

#### II. White Cells.

(a) The white or colorless cells are but little different from the red in color, the latter being so nearly colorless. We first notice them either by their amœboid movements, or because they are not moved by the plasma currents, but stand like a rock round the sides of which the current of red cells is broken. They are slightly larger in most instances than the red cells; but this difference shows less in the fresh specimens where the leucocyte keeps its spherical shape than in the dried and stained preparations, where it is usually somewhat flattened. Their shape is very irregular and their edges often look tattered.

In some leucocytes the amœboid motions are entirely absent. These are the smallest cells, and in them a single nucleus filling most of the cell can often be seen. They are much more nearly spherical and less irregular than the amœboid cells.

The large amoeboid leucocytes are more or less granular, and in certain lights these granules look quite dark and are sometimes mistaken for bits of malarial pigment. This is especially true of the *coarse granular* cells seen occasionally; staining shows these large granules much more distinctly (= eosinophile—see below, p. 65); cells of this type are the most actively amœboid of all.

(b) The most important point in connection with the leucocytes is their ratio to the red cells. This is estimated in fresh specimens not by any actual counting but by reference to a standard fixed in the mind by study of normal specimens, and any considerable increase of the white cells would be noticed at once. Naturally we must not judge from any one part of the slide, as the distribution of the leucocytes may be unequal in different parts of it.

#### III. Blood Plates.

Unless the number of these elements is increased by some pathological influence, we seldom notice them at all in normal blood. This may be because we do not work quickly enough in preparing our specimen. Hayem recommends that the cover-glass be laid

<sup>1</sup>It is probable that the elements included under this heading comprise several different things. It is beyond the plan of this book to discuss their origin and significance, since they possess at present no clinical value.

upon the slide before the puncture is made; as soon as the drop emerges it is allowed to run in between slide and cover by capillary attraction, thus avoiding contact with the air.' The blood plates are irregularly shaped, very cohesive elements, about one-half the diameter of a blood disc, usually seen clinging together in masses like zoöglæa. They are colorless and not amæboid and look like débris.

#### IV. Fibrin Network.

After a specimen of fresh blood has stood for some time exposed to as much air as can creep in between slide and cover-glass, we begin to notice a network of fine straight lines in the spaces between the corpuscles. Here and there these filaments seem to

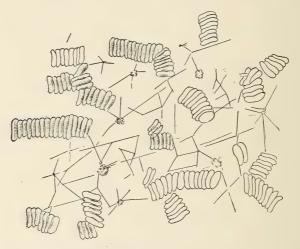


Fig. 23.—Rouleaux Formation and Fibrin Network of Normal Blood.

radiate from a centre where irregular, colorless masses, apparently blood plates, are to be seen (Fig. 23).

No stain is needed to demonstrate these fibrin threads, but a

<sup>1</sup>This is a very satisfactory way if we wish to see the corpuscles as fresh and unspoiled as we can. Put a cover-glass on a slide so that the edge of one corresponds with the edge of the other, and, holding them in this position with finger and thumb, put their superimposed edges into the side of the drop as it emerges. It will run in between them by capillary attraction. The blood plates can be stained with eosin, and in the eosin-hæmatoxylon stain are easily seen and their number approximately estimated.

small-aperture diaphragm and very little light make them plainer. Their only importance is that under certain pathological conditions the fibrin network is very much increased and helps us in the diagnosis (Fig. 24). Hence it is of importance to be familiar with the

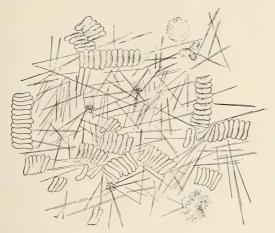


Fig. 24.—Increased Thickness of Fibrin Network.

ordinary closeness of the network in normal blood as a standard of comparison.

For an account of the conditions of its increase see Chapter IX., page 121.

#### AVERAGE DIAMETER OF RED CELLS.

The blood under normal conditions shows considerable variations in the size of its corpuscles in the fresh state as well as in stained specimens.<sup>1</sup>

<sup>1</sup> A method of measuring, approximately accurate, and easily applicable in clinical work is the following:

Using a camera lucida, trace on paper the divisions of a fine stage micrometer as seen under a one-twelfth oil immersion lens; such micrometers are usually ruled to one one-hundredth of a millimetre. Approximate accuracy in our tracing can be obtained if the process is repeated till the divisions marked in successive drawings correspond accurately one with another. Care must be taken that the paper is flat upon the table beside the microscope, and not raised on a block or otherwise; also that the part of the paper on which we draw should be perpendicularly under the centre of the mirror and not off to one side. When a drawing has been made with these precautions, we have only to divide the space between each of the lines in our drawing into

The following table (v. Limbeck) shows the results of various observers.

Normal Li	mits. Average	Diameter
Welckerdiameter $= 4$ .	$5-9.5 \mu$ 7	$\mu$
Valentin		μ
Malinin		7 μ
Hayemdiameter = $6$ -	$8.8  \mu$ ., 7.	5 μ
Mallassez	7.	$6 \mu$
Laache diameter = $6$ -	$-9 \mu \dots 8.$	5 μ
Bizzozero	7.	$075 \mu$
Gram diameter $= 6$ .	$7-9.3 \mu$ 7.	$.850 \mu$
	A 770700 000 - 17	F

Average =  $7.5 \mu$ 

These differences depend partly on differences in the method of measuring (wet or dry), and partly on the fact that the age and conditions of nutrition in the persons selected make a difference. In the new-born, and to some extent throughout childhood, the normal limits of variations are wider than in adults  $(3.3-10.5 \, \mu, \, \text{Hayem})$ . Sex appears to have no constant influence.

Gram<sup>1</sup> noted that the measurements published by observers living in southern Europe are smaller than those of northern Europe (Italians 7–7.5, Germans 7.8, Norwegians 8.5).

The majority of any individual's red cells are certainly about  $7.5\,\mu$  in diameter, and this may accordingly be taken as our standard (Hayem counts twelve per cent under  $6.6\,\mu$ , twelve per cent over  $8\,\mu$ , the rest  $7.5\,\mu$ ).

#### NORMAL NUMBER OF THE RED CELLS.

1. At the level of the sea and in adult life the normal number of red cells per cubic millimetre is about 5,000,000 for men and 4,500,000 for women. This is not infrequently increased in very vigorous, healthy persons; 6,000,000 is by no means rare among

ten equal parts, and we have a scale, each division of which represents 1  $\mu$  as seen under a one-twelfth oil-immersion lens, with the length of tube of the particular microscope used. To use our  $\mu$ -scale we have only to draw with the camera lucida any cell whose size we want to know, using always the same microscope, the same length of tube, and the same lenses, and having the drawing paper (as before) flat on the table and perpendicularly under the mirror. The drawing thus made is measured with the  $\mu$ -scale like any other object.

With this method a cell can be measured in a few seconds and with sufficient accuracy (i.e., within  $0.5~\mu$ ).

<sup>&</sup>lt;sup>1</sup> Fortschritte der Medicin, 1884.

healthy young men, and higher figures are seen occasionally. Thus Hewes¹ in fifty young medical students found an average of 5,809,-000 per cubic millimetre; of these fifteen exceeded 6,000,000, the highest being 6,400,000, while the lowest of the whole series was 5,120,000. Altitude above the sea level raises the count invariably (see page 78).

- 2. The influence of menstruation, childbirth, and lactation is to diminish the red cells temporarily, the amount of the diminution depending not only on the amount of blood lost but on the capacity of the individual organism for blood regeneration. At puberty, when sexual functions are being established, we expect lower counts than after the establishment of the function. Normal pregnancy does not affect the count of red cells.
- 3. The count of red cells per cubic millimetre is raised by any cause inducing concentration of the blood, such as profuse sweating, and is lowered by the temporary dilution of the blood after large draughts of liquid. In these changes, which are always very transient, the hæmoglobin and specific gravity in a given drop are of course increased with the corpuscles.

Vasomotor influences affecting the calibre of the peripheral vessels (hot or cold baths, exercise, etc.) may temporarily concentrate or dilute the blood by affecting the interchange of fluid between the vessels and the surrounding lymph spaces. By these processes the blood in the peripheral vessels may show an increase or diminution in the cellular elements, the hæmoglobin and specific gravity corresponding to the greater or less concentration of the blood at that point (on these points see below page 76).

Hayem noted that in young people especially the number of red cells varied considerably without any notable change in conditions.

## 4. Influence of Nutrition on the Number of Red Cells.

A. After a meal, especially when considerable liquid is taken, the blood is temporarily diluted and hence the count of red cells per cubic millimetre is diminished (v. Limbeck; Reinert). This is illustrated by the following case from v. Limbeck.

ADULT, MALE, HEALTHY.

Red Cells. White Cells. Hb
11:15 A.M...... 5,530,000 7,660 98 per cent.
12 M. dinner

<sup>&</sup>lt;sup>1</sup> Transactions of the Boston Society of Medical Science, May 18, 1897.

		Red Cells.	White Cells.	Hb
12:15 P	. M	 5,320,000	6,166	
1:15	66	 5,480,000	8,500	
2:15	66	 4,733,000	12,000	
3:15	66	 4,872,000	14,000	89 per cent.
4:15	66	 4,720,000	10,830	89 "

As the white cells rise (digestive leucocytosis, see below, page 97) the red fall.

Fasting, by concentrating the blood, temporarily increases the number of red cells (400,000-500,000 increase after twenty-four hours' fast).

B. General Nutrition.—Lean, muscular people have on the average more red cells per cubic millimetre than fat people (Leichtenstern, quoted by v. Limbeck), other things being equal.

As above said, fasting (by concentrating the blood), raises the number of red blood cells, so that it is not simply hunger that gives us the *diminution* in red cells commonly found in *poorly nourished* people, but rather the influence of bad hygiene in the slums, etc.

- 5. Seasons and the time of day seem to have no influence in themselves. The same is true of race and elimate. The only exception to this is reported in the work of E. Below, who found in yellow-fever districts an average count of only 4,700,000 red cells per cubic millimetre and the diameter of the individual cell reduced to  $5.9~\mu$  on the average  $(7.5~\mu={\rm normal})$ .
- 6. Fatigue.—Hayem noted a loss of from 500,000 to 1,000,000 red cells per cubic millimetre in the blood of a number of farmers after a hard summer's work, the counts made in September having been compared with those of April and always found to be lower. Whether fatigue is the only cause of this diminution may be doubted.
- 7. Age.—In the new-born the number of red cells is very high for a few days (7,000,000 to 8,800,000), but falls at the end of seven to ten days (see page 445).

In the very old a certain degree of anæmia is, so to speak, physiological; but this, which like the plethora of the new-born is to be referred *not* to the fact of age, but to concomitant influences, is by no means invariable. Schmaltz reports 6,766,000 red cells in a man of eighty-one and 4,816,000 in a woman of seventy-four.

<sup>&</sup>lt;sup>1</sup> The influence of stasis in the obese, whose fat loads the surface of the heart, is to cause an apparent increase of red cells.

<sup>&</sup>lt;sup>2</sup> "Deut. Tropenhygiene," Berlin, 1895. O. Coblanz.

<sup>&</sup>lt;sup>2</sup> See also under Anchylostomiasis, p. 428.

#### NORMAL NUMBER OF WHITE CELLS.

The figure usually given for adults is 7,500 per cubic millimetre. This varies a good deal, according to the nutrition of the individual (see page 95) and also at different times of the day, owing to influences not explained. The influence of digestion will be mentioned later. In animals a slight shock is sufficient materially to affect the count of leucocytes; 5,000 to 10,500 may be called the normal limits. Romberg finds 9,058 as the average count in fifty-five healthy young women. There is, I believe, no evidence to show whether or not mental disturbances (fear, rage, emotion of various kinds) affect their number, but my impression is that they do. Other causes of variation will be discussed under Leucocytosis.

#### BLOOD PLATES.

The number of blood plates is variously estimated at from 180,000 –250,000 (v. Emden) to 860,000 (Kemp and Calhoun). They do not contain hæmoglobin and show no signs of a nucleus. They are the chief constituents of white thrombi. Wherever they are diminished (e.g., in hæmophilia, purpura) clotting is apt to be slow, and there is reason to believe—

- (a) That their number is an index of lowered resistance of the red cells.
- (b) That whenever their number is much increased, thrombosis is likely to occur. In chlorosis, for instance, their number is increased and thrombosis is relatively common, while in pernicious anæmia they are diminished, and thrombosis rarely if ever occurs.

Coagulation time outside the body depends largely on the amount of fibrin and is a wholly different phenomenon from intravascular thrombosis. This is of importance in connection with the use of gelatin injections to favor thrombosis in aneurisms. An increased rapidity of coagulation outside the body is no indication of success in such cases. Blood plates are increased in leukæmia and in many cases of grave anæmia. In the severer types of many infections (typhus, erysipelas, malaria) they are diminished, and in malaria they are sometimes wholly absent during the fever. In pneumonia and tuberculosis they are normal or increased. In purpura and hæmophilia they are sometimes much diminished or absent.

<sup>1</sup> Löwit: "Studien z. Physiol. und Pathol. d. Blutes," etc., Jena, 1892 Fischer.

The physiological limits of the amount of hæmoglobin and of the specific gravity have already been mentioned. Under physiological conditions their variations follow those of the count of red cells.

### MÜLLER'S "BLOOD DUST."

Müller has recently described under the title of "Hæmoconien," or blood dust, a constituent of normal and pathological blood not hitherto noticed. This consists of small round colorless granules about the size of the finest fat drops—or about  $\frac{1}{1}$ —1  $\mu$  in diameter, their size being very variable. They are highly refractile and have rapid dancing (molecular) motion, but no power of locomotion. They are insoluble in alcohol and ether, not stained by osmic acid, and take no part in the formation of fibrin. Stokes and Wegefarth,2 who have confirmed Müller's observations, note that the "blood dust" can be seen much more clearly by the light of a Welsbach gas burner than by daylight. The latter observers present a body of evidence tending strongly to show that these bodies are the extruded granules of neutrophilic and eosinophilic leucocytes. ules apparently identical with them can be stained in fresh specimens with eosin or Ehrlich's triacid stain in a way apparently like that of the intracellular granules.3 They are also to be seen in pus and in hydrocele fluid.

No special diagnostic or prognostic significance has yet been attached to them, though the work of Kanthack and Stokes renders them of great interest with reference to the problem of immunity.

<sup>&</sup>lt;sup>1</sup> Centralbl. für allg. Path., etc., viii., 1896.

<sup>&</sup>lt;sup>2</sup> Johns Hopkins Hospital Bulletin, December, 1897.

<sup>&</sup>lt;sup>2</sup> Nicholls: Phil. Med. Jour., Feb. 26, 1898.



#### PLATE I.

- Fig. 1.—(a) Polymorphonuclear Neutrophiles. Note the varieties in size and shape of granules, the irregular staining of the nuclei, the light space around them, their relatively central position in the cell.
- (b) Myelocytes. Note identity of granules with those just described; the even, pale stain of nuclei; their position near the surface (edge) of the cell. The two cells figured indicate the usual variations in the size of the whole cell.
- (c) Small Lymphocytes. In the cell at the left note transparent protoplasm; in the cell next to it note very pale pink of protoplasm around nucleus which is deeply stained, especially at the periphery. The next cell has an indented nucleus; its protoplasm relatively distinct. The cell on the extreme right shows no protoplasm and is probably necrotic. In all note absence of granules with this stain. With basic stains a blue network appears in the protoplasm.
- (d) Large Lymphocytes. Note pale-stained nuclei and protoplasm, irregularity of outline; indented nucleus in one. Every intermediate stage between these and the "small" lymphocytes occurs, and the distinction between them is arbitrary.
- (e) Eosinophile. Note irregular shape, loose connection of granules, their copper color, their uniform and relatively large size, and spherical shape.
- (f) Eosinophilic Myelocyte. Note similarity to (b) ordinary myelocytes except as regards granules. Color of granules may be as in (e) ordinary eosinophile.

All the above were stained with the Ehrlich triacid stain, and drawn with camera lucida. Oil-immersion objective one-twelfth and ocular No. iii. (Leitz).

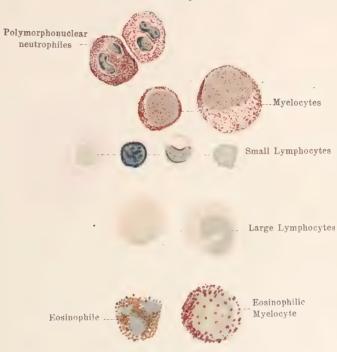
- Fig. 2.—Malarial Parasites in Fresh (Unstained) Blood (Tertian Forms). N,N, normal red corpuscles; 1, red cell containing hyaline body; 2, 3, 4, 5, successive stages in the development of the parasite, showing acquisition of pigment; 6, 7, full-grown parasites, the corpuscle no longer visible; 8, beginning of segmentation; 9, segmentation. In 6 and 7 note brownish blur behind the pigment dots. Drawn as in Fig. 1.
- Fig. 3.—Tertian Parasite Stained with Eosin and Methyl Blue. The remains of the corpuscle containing the parasite stain pink, the parasite blue, and its pigment black. The stages of growth correspond with the numbers attached. Note in Figs. 1, 2, 3, and 4 the shape of the parasite, shown better than in fresh specimen.

[Owing to a mistake the cells in Fig. 3 are not drawn according to a single scale and their relative sizes must be disregarded.]

## Examination of the Blood.

#### PLATE I.

Fig. 1. Varieties of Leucocytes.



### The Malarial Organism.

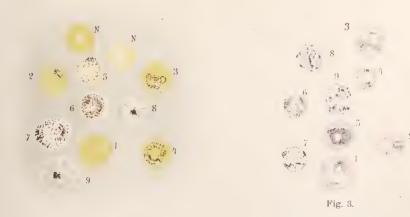


Fig. 2.



#### CHAPTER V.

#### FINER STRUCTURE OF THE BLOOD.

APPEARANCES OF DRIED AND STAINED SPECIMENS.

COVER-GLASS specimens prepared and stained as above directed give us more information of interest and importance than can be obtained from any other one method of blood examination. Approximate ideas of the quantity of red cells, of white cells, and of hæmoglobin can be formed, parasites and bacteria can be seen, and the whole mass of evidence based on the finer structure of the leucocytes can be obtained only in this way. The appearances of a specimen of normal blood prepared in this way are as follows:

#### RED CELLS.

1. The hæmoglobin stains with the orange G of the tricolor mixture, and in a properly heated specimen the red cells are of a brilliant yellow or pale orange tint. If overheated they have a feebly stained, washed-out look, while if underheated they are more or less brown or gray.

The degree of pallor of the centres corresponding to the amount of hæmoglobin in the corpuscle can be gauged much more accurately with this stain than in the fresh preparations. The color of the edges is not much affected by pathological changes, the centres being the test. But in cases with extreme poverty of hæmoglobin the colored rim may be reduced to a mere shell and the rest may be almost completely colorless. The power to estimate the amount of coloring matter in this way can be easily acquired.

An approximate idea of the number of red cells may be formed by any observer who has learned to use a uniform technique in each case and to spread the blood of a standard thickness.

2. Nothing is seen of the fibrin or blood plates as a rule. In

<sup>1</sup> This is a fruitful source of error. Many suppose that because their specimens come out too dark they must be "burnt," and so heat less. In fact the dark tint means that the specimen is not heated enough.

normal cases the plasma does not stain at all. A certain amount of débris is often present, usually pink stained.

#### WHITE CORPUSCLES.

3. The chief purpose and use of the "triple stain" is for distinguishing the varieties of white corpuscles, and the pathological states of the red. About the normal red cells it gives us no information that cannot be obtained as well by various other stains, but our knowledge of normal leucocytes has been immensely enlarged by its use.

In normal blood, stained as above directed, we recognize the following varieties of white cells:

(1) Small lymphocytes or "small hyaline forms" (Kanthack) (see Plate I.). These consist mostly of a round blue nucleus about the size of a red cell, surrounded by a thin coating of protoplasm, which is faintly stained or invisible with Ehrlich's triple stain, but stains dark patchy blue when Hewes' blue counterstain is used.

The nucleus may be considerably smaller than a red cell. With ordinary triple stain it is usually pale-stained, but when a blue counterstain is used it stands out intense indigo color. This is one of the greatest merits of Hewes' after-stain. Without it the lymphocytes are often so pale that some of them may be overlooked in counting.

The unequal staining of the protoplasm with the methylene blue is probably not a true granulation but a reticular structure.

(2) With Ehrlich's triacid stain I do not find it possible to draw any line between this form and that now to be described, namely, the "large lymphocyte" or "large mononuclear cell," which is simply larger and paler.

The small lymphocyte is the form most frequently seen in the lymph channels, in chyle, and at the periphery of the follicles of adenoid tissue. In the so-called "large lymphocyte" the nucleus occupies relatively less of the cell than in the small lymphocyte and stains less readily.

In many cases we do not see in the blood any intermediate forms. Lymphocytes are either "small" (5–10  $\mu$  in diameter) or "large" (13–15  $\mu$  in diameter) (see Plate I.).

In other cases we find every intermediate size, both of nucleus

and of the cells as a whole, and in such cases I am unable to make a division into "large" or "small," though we may be able to say in a general way which size predominates. The edges of the larger forms are often frayed and jagged, and small bits may bud off and circulate as free elements. This is especially frequent in lymphatic leukæmia.

The theory that the "large" mononuclear cells or "large hyaline forms" (Kanthack) come from the spleen and the small mononuclear from the lymph glands has been abandoned on all sides of late years.

The protoplasm of all lymphocytes, as has been said, is always hard to stain with Ehrlich's triple stain. Sometimes it has a faint pinkish tinge, more frequently it is grayish or very light blue, and in some cases it stands out brilliantly transparent and colorless against the faint purplish tinge of the surrounding plasma (see Plate I.). When a blue after-stain is used an artificial retraction ring of unstained protoplasm appears around the nucleus. Sometimes the protoplasm stains diffusely blue with basic stains and no network can be made out.

I have described the lymphocytes so far as "mononuclear," but it is not rare to find even very small ones (6  $\mu$  in diameter) whose nucleus has a deep cut in one side or has divided into two parts. I believe it is commoner to find a divided nucleus in the small forms than in the "large lymphocytes." The inapplicability of the term "small mononuclear cells" or "large mononuclear cells" to this variety of corpuscle is evident. The distinguishing mark is not the single nucleus. (See also below under "Mast cells.")

Ehrlich separates sharply under the name of "large mononuclear leucocytes" a group of cells closely resembling the larger forms of lymphocytes. Taylor and other first-class authorities agree with him in this, but their descriptions include so few differentiating marks that I am unable to recognize them. As they make up but one per cent of the white corpuscles and have no clinical significance, I have grouped them in my counts with the large lymphocytes. I have done the same with the so-called

3. "Transitional forms" (Ehrlich), which are no bigger than the larger type of lymphocytes, from which they differ only in that they have an indentation in their nucleus—either a narrow cut or a bay so wide that a "horseshoe" nucleus results. This is the transitional form according to this nomenclature. There is no reason for

calling it so, as all the forms of leucocytes are transitional, but there is some convenience in the name. Like most large lymphocytes it is pale all through—pale in both nucleus and protoplasm—and often escapes notice in hasty examinations. Sometimes its protoplasm is sparsely covered with faint neutrophilic granules.

4. The cells known as "polynuclear" or polymorphonuclear neutrophiles. These cells constitute the vast majority of those found in ordinary pus. The main difference between them and those last described is in the possession of granules, best seen when stained by Ehrlich's methods. The nucleus stains deeply with all dyes. It is very irregular in shape, being twisted about in the body of the cell. Here and there it may dive down so deeply beneath the surface of the cell that it is hidden under a thick layer of granules, reappearing in another part of the cell so that it seems to be broken in two. Occasionally, no doubt, this is actually the case, but generally there are "underground connections" between the apparently separate pieces of nucleus. Now and then we see a cell (degenerating) where the granules have fallen away, leaving the nucleus like a short, thick snake, very rarely two, or like several sausages joined by strings.

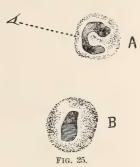
One never sees any two of these cells whose nuclei are of the same shape. Hence the term "polymorphonuclear." The windings and twistings of the nucleus have suggested comparisons to the letters Z, S, E, etc.

The granules which fill the body of the cell and in which the nucleus is embedded stain best with triple stains like Ehrlich's. Acid stains like eosin, and basic stains like methylene blue, do not bring them out clearly. Hence the term "neutrophilic," which is not strictly accurate; more properly they are faintly oxyphilic¹ and can be faintly stained with eosin. [Hence Kanthack and other English observers have called them "fine granular oxyphiles," while the term "coarse granular oxyphiles" is applied to the cells generally known as eosinophiles. These terms are in some respects more accurate than Ehrlich's, but are even more cumbrous than his.] With Ehrlich's triacid mixture the granules stain violet or purple, sometimes pink, their color varying apparently according to their age. The older the granule the pinker. The younger it is, the more violet affinity it has (see below, p. 69). The granules are very small and irregular in shape and size, contrasting with the

<sup>&</sup>lt;sup>1</sup> Ehrlich's stain is really a differential acid stain and not neutral.

large, round, "eosinophile" granules (see below). The cells being spherical the granules lie *over* and around the nucleus, not simply at the side of it. In their interstices we sometimes seem to see a pinkish background of cell substance. In normal blood these "neu-

trophilic" granules, which are so small that except with very high powers they look like a diffuse stain, very rarely occur except in cells whose nucleus has reached the polymorphous stage. Occasionally we seem to see mononuclear neutrophiles, having a round nucleus with neutrophilic granules, but careful focussing usually shows that the appearance of a round or rod-shaped nucleus is given by the tight coiling of the ribbon-like nucleus round



one of its ends, or else that a horseshoe nucleus is seen from the point of view indicated in Fig. 25. Thus if the eye be at the point A the nucleus will appear of the shape indicated in B (Fig. 25).

5. The eosinophile or "coarse granular oxyphile" cell has, like its predecessor, a polymorphous nucleus and granules; but the nucleus is paler and more loosely connected to the granules, and the latter are spherical or oval, of nearly uniform size, and much larger than any seen in the neutrophilic cell. They have strong affinity for acid coloring matters (eosin, acid-fuchsin, etc.), hence their name. In specimens stained with eosin or eosin and methylene blue they are very brightly colored pink. With the triacid mixture they are of a copper or burnt-sienna color. Some individual granules stain much darker than others in the same cell.

The eosinophiles are the most actively amœboid of all the corpuscles, and it may be for this reason that the different parts of the cell seem so loosely strung together. Or, if the hypothesis of Kanthack and Hardy, recently supported by Stokes, be true, their loose arrangement may serve to make them easily detached for bactericidal purposes (see above, page 60). The granules may be all at one side of the cell and the nucleus on the other, and in cover-glass specimens we very frequently find actual separation of the two. Whether or not the actual separation is brought about by the technique of spreading the blood is unimportant, as we find such broken cells much more often among the eosinophiles than among any other variety—which argues a looser structure.

Sometimes there seem to be two or more distinct and separate nuclei in the cell, no "underground connection" being traceable. The granules are seldom *over* the nucleus as we see it in cover-glass preparations, but cluster round it loosely.

The cell as a whole is usually a little smaller than the "neutrophile" and more irregular in shape. In stained specimens the neutrophile is seldom seen with a pseudopod extended, whereas the eosinophile often shows it.

The staining of the nucleus is more even as well as paler than that of the neutrophile, and with the Ehrlich stain often has a robin's-egg tint. To sum up:

The four varieties which we usually find among leucocytes in the blood are these:

- 1. Small lymphocytes, or "hyaline cells."
- 2. Large lymphocytes and transitional forms.
- 3. Polymorphonuclear neutrophiles, or fine granular oxyphiles.
- 4. Eosinophiles, or coarse granular oxyphiles.
- 5. A fifth variety of leucocyte—the basophilic "mast cell" is a constituent of normal blood, though in very small numbers. One-half per cent is the maximum number in health. In leukæmia it is common, but no special significance is attached to it. Taylor found it in increased numbers in one case of cancer, one of gonorrhea, one of mycosis fungoides, and two of septic bone disease. Canon has found a similar increase in chlorosis and some chronic skin diseases, and I in trichinosis.

With Ehrlich's stain the basophilic granules of this cell are not seen or appear only as clear white spots. They are best stained with thionin or toluidin blue. The nucleus is polymorphous, often trilobed.

#### TERMS.

No one can feel more unsatisfied with the terminology used in this book than the writer. It rests partly on a theory of the origin of the cells ("lymphocytes"), partly on the properties of the nucleus ("polymorphonuclear"), and partly on affinities for aniline dyes ("neutrophile"—"eosinophile").

All that can be said for it is that it discards certain very misleading names like "splenocyte" (a term applied by some to the large lymphocytes according to the now exploded theory that they come from the spleen), or like "small mononuclear" to designate cells not rarely polynuclear.

The cumbrous word "polymorphonuclear" is a shade better than "polynuclear," and that is all to be said in its favor.

It is greatly to be hoped that we may ere long have a new and improved terminology by some competent student. The English terms above referred to are so cumbrous that I have not as yet felt compelled by their slightly greater accuracy to adopt them unconditionally, but they certainly show a tendency in the right direction.

### Origin of the Different Varieties.

Two groups may be distinguished:

- I. The myelogenous group (from the bone marrow).
- (a) Polymorphonuclear neutrophiles.
- (b) Eosinophiles.
- (c) Mast cells.
  - (d) Large mononuclear cells (Ehrlich)??

II. The lymphogenous group (from adenoid tissue).

Lymphocytes of all sizes.

Except within Group II. no transitions between the different varieties of circulating leucocytes are recognized.

### NORMAL PERCENTAGE OF EACH VARIETY.

In the blood of healthy adults the proportions of the different varieties above described are the following:

(Small lymphocytes	20-30	per cent.
(a) { Small lymphocytes	4-8	- "
(b) Polymorphonuclear neutrophiles	62-70	66
(c) Eosinophiles	$\frac{1}{2}-4$	44
(d) "Mast cells"	$\frac{1}{40} - \frac{1}{2}$	46

(a) In infancy the percentage of lymphocytes is much larger (forty to sixty per cent) and the polymorphonuclear neutrophiles are only eighteen or forty per cent.

In a variety of debilitated conditions not usually thought of as definite diseases, the percentage of lymphocytes is comparatively large and that of the polymorphonuclear cells small. The general vigor and health of the individual can sometimes be estimated simply from the leucocytes. Persons calling themselves well, but never vigorous or active, may show no more than fifty per cent of polymorphonuclear cells, the lymphocytes running up to forty, fifty, or

 $<sup>^{\</sup>rm I}$  This change is usually dependent on an absolute diminution in the myelogenous cells.

even seventy-five per cent. In an unmarried woman of twentynine, suffering from no discoverable organic disease, I found one day among 1,200 leucocytes 74.9 per cent of lymphocytes with only 25 per cent of polymorphonuclear cells. The total leucocyte count was 6,000 per c.mm. Two weeks later the percentages were normal, although no change had been observed in the patient's (debilitated) condition. She is now well and married.

Not all cases of debility show this change, and we are not yet in a position to say under just what conditions it occurs. It certainly is not peculiar to tuberculosis as Holmes has supposed. Presumably the conditions are such as decrease the functional activity of the marrow.

- (b) Changes in the percentage of neutrophiles will be discussed later.
- (c) The percentage of eosinophiles often changes in a way hard to explain. Their increase or decrease in the circulating blood does not follow that of the polymorphonuclear neutrophiles, in fact is often inversely proportional to it, and the eosinophiles may be markedly increased in a blood otherwise normal, for reasons wholly unknown to us.

An increase in the lymphocytes or neutrophiles rarely occurs without other blood changes, and points, not to disease of one place or function, but to general conditions like inflammation or malnutrition. The diagnostic indications of an increase of the eosinophiles are more specific (ride infra, articles "Trichinosis," "Asthma," "Dermatitis Herpetiformis," etc.).

The eosinophiles and "mast cells" may be pictured as comparative strangers, though not intruders in the circulating blood. They are thus intermediate between the regular inhabitants (lymphocytes and neutrophiles) and the variety next to be mentioned, which are real intruders—i.e., almost never found in normal blood. These are the

#### MYELOCYTES.

The larger portion of the leucocytes of the marrow is made up of mononuclear neutrophiles, a type of cell not yet described, and differing from any variety found in normal blood, although it has many points of resemblance to the polymorphonuclear neutrophile, and is in fact the same cell in an early stage of growth.

I describe it here because it is peculiar to no one disease and is an occasional visitor of the blood in various diseased conditions and in conditions on the borderland between the pathological and the physiological (starvation—various intoxications).

The myelocyte (see Plate I.), like its descendant, the polymorphonuclear neutrophile, is recognizable only by Ehrlich's staining methods. With Ehrlich's triple stain it appears as a spherical cell nearly filled by a large, pale-stained nucleus immersed in neutrophilic granules. One sees at once how little it differs from the large lymphocytes (simply in having granules) and from the polymorphonuclear neutrophile (only in the shape of its nucleus). have called the granules neutrophilic, and this is true of the great majority of them in most cells. But as Ehrlich has recently pointed out, there is a great deal of variation in the staining affinities of different granules, side by side, in the same cell. In some granules (according to Ehrlich the younger ones) "there is prominent a basophil portion which becomes less and less marked as the cell grows older." Such granules take with Hewes' after-stain a bluish tint. Others near them (older?) are violet, while others again are nearly pink. In the polynuclear neutrophile these basophile affinities are much less marked, but even in them considerable differences may be made out between the tints of adjacent cells and of adjacent granules in the same cell. In size and shape the myelocyte granules are like those of the polynuclear cell (see Plate I.). The nucleus, by which we chiefly distinguish the myelocyte, shows none of the twists and turns characteristic of the polymorphonuclear neutrophile, but is usually spherical or egg-shaped, and is in close contact with the cell wall for a comparatively large portion of its extent—i.e., if egg-shaped it is placed eccentrically.

Not infrequently the nucleus shows signs of old age (vacuoles) or of mitosis, for occasionally we find two nuclei at the poles of the cell.

## Size of Myelocytes.

All the older accounts of the myelocyte speak of it as a very large cell, the largest variety of leucocyte ever seen in the blood.

This is true of many of them; diameters of  $18-21~\mu$  are not uncommon, but we also find them of *every* other size down to  $10-11~\mu$  diameter, that is, down to the size of a lymphocyte. This holds both for the myelocytes in the circulating (leukæmic) blood and for

those in the marrow. No distinction from other varieties of leucocyte can be based on size alone, unless we say their *average* size is greater than the average size of the leucocyte. Perhaps the following table may be of interest:

Average diameter of 100 myelocytes = 15.75  $\mu$ .

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" " 100 polymorphonuclear neutrophiles = 13.50 \mu.
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" " 100 "large" lymphocytes = 13  $\mu$ .

" 100 eosinophiles =  $12 \mu$ .

" " 100 " small " lymphocytes =  $10 \mu$ .

" " 100 red corpuscles (normal) = 7.5  $\mu$ .

#### Eosinophilic Myelocytes.

Under the same conditions which favor the appearance of the ordinary (neutrophilic) myelocyte, we often find a small number of cells identical with them in all respects, except in possessing eosinophilic in place of neutrophilic granules. Such cells are found in abundance in the marrow, and this fact together with the resemblance to the ordinary myelocyte both in morphology and in the conditions of their occurrence, seems to me to justify the term eosinophilic myelocyte. In them as in all myelocytes there is a wide variation between the staining affinities of different granules, some being much darker than others.

So far I have described the *type cell* of each variety. As we should expect, atypical forms are numerous. Some of the commoner ones are as follows:

### I. DEGENERATED LEUCOCYTES.

Frequently in leukæmia and occasionally in other conditions one sees leucocytes apparently moribund. That they are not always artifacts is shown by the fact that they are not found in normal blood treated by the same technique that reveals them in the blood and in hardened blood clot of leukæmic cases as well as by the fact that Botkin and others have produced similar appearances by keeping the leucocytes a few days in an aseptic state.

The commonest forms of degenerated leucocytes are:

- 1. A homogeneously stained mass looking like a washed out, structureless nucleus that has lost its protoplasm and become ragged at the edges (karyolysis).
  - 2. The same intensely stained.

3. Vacuolization of the nucleus or of the protoplasm.

All these forms of degeneration affect chiefly the lymphocytes and large mononuclear forms. In the granular leucocytes we see all stages of breaking up; the granules are scattered about the field and the nucleus is pale, structureless, and deformed.

#### II. TRANSITIONAL NEUTROPHILES.

Cells on the borderland between the "marrow cell" and the "polymorphonuclear leucocyte," the nucleus having some of the characters of each variety (see below, p. 110).

#### III. Turck's "Stimulation Forms."

These cells are also described by Engel as "mononuclear cells" and very recently by Weil as "non-granular myelocytes."

Weil's description conveys the salient points in the appearance of this cell. It looks like a myelocyte whose granules have been fused into a smooth homogeneous band of color around the single spherical or ovoid nucleus. The protoplasm is always homogeneous and deeply stained; there is, however, a good deal of variation in the tint in different cells. In some it is purple, in others violet or brown. In leukæmia they are often counted as myelocytes or as large lymphocytes by unpractised observers.

They appear in various diseases associated with *stimulation of* the bone marrow, i.e., grave anæmia and all conditions associated with leucocytosis (see below, p. 110).

Other rare varieties will be mentioned under leukæmia.

# PART III.

## GENERAL PATHOLOGY OF THE BLOOD.

### CHAPTER VI.

UNEQUAL DISTRIBUTION OF BLOOD—POLYCYTHÆMIA—DILUTION AND CONCENTRATION OF THE BLOOD.

### 1. Unequal Distribution.

How far is the single drop used for blood examination typical of the whole?

It has been experimentally proved that specimens of the blood of the smaller venous and arterial twigs do not differ from each other materially in corpuscular richness. Capillary blood is slightly richer in corpuscles than that either of veins or of arteries. But as capillary blood is everywhere of the same corpuscular richness, we may consider one capillary network or set of venules as typical as another, provided our technique is good, that is, provided lymph is not squeezed into the drop by strong pressure. It is indifferent, therefore so far as accuracy is concerned, whether the drop of blood be obtained from one or another part of the body. All standard estimates of the number of corpuscles per cubic millimetre of normal blood refer to capillary blood.

## 2. Local or Peripheral Polycythæmia.

So far we are speaking of normal conditions. It is a familiar fact, however, that the vessels of a given part of the body can be overcrowded with blood, e.g., by the use of an Esmarch bandage. A drop taken from such a part would certainly not be typical. Now as the same effect can be produced by a variety of diseases,

under these conditions we must modify considerably any inferences made from examination of a single drop.

Such conditions, entailing a false polycythæmia or apparent increase in the number of corpuscles are:

Any disease involving either (a) general cyanosis or (b) cyanosis of the part from which the drop of blood is drawn.

(a) General cyanosis results from cardiac insufficiency (valvular or parietal disease of the heart itself, blocking of the lung circulation by emphysema or thrombosis), from insufficient aëration of the blood (pneumonia, congenital malformation of the heart), interference with the heart's action by pressure of tumors, effusions (pericardial, pleural, peritoneal), or enlarged organs (liver, spleen), or from vasomotor disturbances. It is evident that some of these conditions (e.g., congenital heart disease) may not involve any peripheral stasis at all, and in the absence of this it is not easy to account for the increased number of corpuscles in the drop. Some observers have supposed that there is a real overproduction of blood cells under these conditions; others suppose that the life of the individual corpuscle being lengthened, reproduction of cells at the normal rate soon leads to the "glut." There seems to be no reason to suppose that there is in these cases any unequal distribution of cells in favor of the periphery, such as is obviously the condition in ordinary cyanosis with stasis. Whatever the explanation may be, there is no doubt of the fact that general cyanosis from any cause whatever produces an increase of cells in a drop such as we usually examine.

The cases of cyanosis which I have classed under "vasomotor" (for want of a better explanation), cases in which, in the absence of disease in any organ, the skin and mucous membranes are persistently and markedly bluish, are not very uncommon. I have seen three such, all in stout, elderly women. In one the cells in a drop of blood from the ear, finger, or toe were more than *double* the normal number (see below, page 75).

(b) Local Cyanosis.—The pressure of a tumor, or any other hindrance to the circulation of any part, may give a similar increase in the number of corpuscles in a measured amount of blood from that part. In paralyzed patients the count may be higher on the paralyzed side.

In markedly cyanotic patients the count of red cells may be notably above normal, and we must make allowances. Error is more

likely to arise when we have cyanosis in a person whose blood is poor in red corpuscles. The combination of these two factors may give us a normal blood count and lead us to overlook the anæmia. Thus a person might have really a severe anæmia and yet the count of red cells be actually above the normal. This element of stasis should never be lost sight of. Many high counts reported in pneumonia or hysteria are to be explained by abnormalities not of production or destruction but of distribution of the blood cells.

With these exceptions the drop of blood taken at the periphery is typical. We have next to consider some *general* conditions under which a person's whole blood may be inferred to be abnormal from the findings in a drop taken from the periphery. Consideration of *special* diseases will follow later.

Temporary increase or diminution in the amount of fluid within the vessels can be brought about not only by a change in the mechanical conditions of pressure and osmosis, but by any influence affecting the tone of the peripheral vessels. We have then:

## Temporary Serous Plethora or Dilution of the Blood

- (a) From transfusion of fluid in large amounts or its ingestion by mouth or rectum.
- (b) From decreased blood pressure, as in acute failures of compensation in cardiac disease.
  - (c) From vasomotor dilatation.

As an example of this last Grawitz reduced the specific gravity of the blood from 1041 to 1038.7 within eight minutes by the inhalation of nitrite of amyl. This decrease of specific gravity can only mean an increased amount of watery constituents in the blood, as there was no evidence of any destruction of the heavier elements of the blood, and only water (and chlorides) pass through the vessel walls easily. In the above case the specific gravity was again at 1041 within a few minutes.

## Polycythæmia.

The red-faced persons popularly known as "full-blooded" show no abnormalities in their blood discoverable by any means of investigation known to us. The condition is probably dependent on the presence of a rich capillary network near the surface of the skin, or a dilatation of individual venules and arterioles at the periphery. Such a person may be markedly anæmic without any considerable changes in the color of the face. The fact that people of such complexion often end their lives with a ruptured cerebral artery is due presumably to the circumstance that "high living" produces in the same individual dilated peripheral capillaries and weakened arterial walls.

Examples of what seems more likely to be a true polycythæmia are as follows:

- (a) In cases of severe anæmia which recover, the blood regeneration may attain such vigor that the number of red cells shoots temporarily up above normal, even as high as 7,700,000.
- (b) The same condition can be temporarily produced by transfusion of actual blood from one individual to another. It lasts but a few days as a rule.
- (e) Some cases occur without any known cause. In one such case which came to autopsy (death from cerebral hemorrhage) the internal organs were as deeply engorged as the periphery of the body. The three cases of the following table are apparently of this type.

The polycythæmia of the new-born, of high altitudes, and of phosphoros poisoning will be discussed later.

Age.	Sex.	Red cells.	White cells.	Hæmo- globin.	Remarks.
29		8,484,000	15,000 17,600	85	February 5. Polynuclear, 84.6; lymphocytes, 13.8; eosinophiles, 1.6. February 8. Polynuclear, 90.4; lympho-
56		6,240,000 4,680,000	10,000 5,600	65 70	cytes, 8; eosinophiles, 6; myelocytes, 1. First day. Eighth day.
53		11,352,000 9,260,000 10,060,000	8,300	105 105 110	December 6. December 7. After walking.
			10,400 a.c. 11,700 p.c.		December 11.
		10,230,000	8,800	110	December 17. Polynuclear, 77.25; lymphocytes, 18.75; eosinophiles, 2.75; myelocytes, 1.25; microblasts, 2; normoblasts, 2. Few mast cells.

TABLE I.—POLYCYTHÆMIA.

# $Concentration \ of \ the \ Blood.$

It is obvious that influences opposite to those producing temporary full-bloodedness will produce temporary lack of fluid within the vessels. So acute diarrhœa, purgation, deprivation of liquids (as in starvation), rapidly accumulated serous effusions, profuse vomiting or sweating (by skin and lungs) produce a temporary concentration of the blood by draining out its diffusible elements (water chiefly) (see Table II.). All these influences are transitory. More permanent drains on the system, like chronic diarrhœa, diabetes insipidus or mellitus, or long-standing suppurations, show no evidence of lessening the volume of blood in the vessels. They drain albumin out of the serum and corpuscles and so decrease the weight of the blood (see below, page 83), but the blood volume is not changed. Indeed, any influence has to work very quickly in order to concentrate the blood, for in an astonishingly short time the other tissues repay the vessels their loss of fluid and the normal blood volume is restored.

The same temporary effects can be produced by influences constricting the vessels (cold, pain, suprarenal extract), and a concentration of the blood results which lasts a few minutes or hours.

In all these interchanges of contents between the blood-vessels and the other tissues it is, as above said, the watery elements chiefly that change. The red cells are not affected by the give-and-take of the vessels and tissues, and although cold produces in the peripheral circulation an increase in the number of white cells greater than can be accounted for by simple concentration, the weight of evidence seems to be against any new production of cells and in favor of a change only in distribution, the white cells accumulating at the periphery.

Now as the number of cells is not affected by these temporary variations in the volume of liquid within the vessels, it follows that the number to be counted in a cubic millimetre, though typical of the whole blood at that time, is not to be reckoned from in the ordinary way. For example, after a severe diarrhea or in phthisis after a night-sweat the blood may be temporarily so concentrated that we find 6,000,000 or more red corpuscles per cubic millimetre. Under normal conditions of the blood mass we should infer from

Oliver has shown recently (Lancet, June 27th, 1896) that any influence causing rise of blood pressure will slightly concentrate the blood. Thus raising the arm over the head and holding it there by muscular effort slightly concentrates the blood in that arm. Electrical stimulation or massage of the arm has the same effect. *Lowering* blood pressure, as when the arm is supported *passively* over the head, dilutes the blood. This confirms the results of Mitchell (Med. News, May, 1893) and of Chéron (Comptes Rend. de l'Acad. d. Sciences, 1896, No. vi.).

such a count that the body contained one-sixth more red corpuscles than usual. Here obviously it means only (if anæmia is absent) that the blood mass is reduced one-sixth by concentration. It is only in such sudden reductions of blood volume that we can measure the amount lost by this method. Long-standing causes of drain on the plasma might at any time act as destroyers of red corpuscles as well, through the changes in the nutritive fluids in which they live.

Further, it is only when we know the number of corpuscles just before the sudden drain on the plasma comes, that we can measure the amount of plasma lost by the amount of apparent increase in the red cells. Stasis and any other cause that heaps up corpuscles at the periphery must also be excluded before we can judge of the loss of plasma in this way.

The conditions of an abnormal concentration of the blood are those already alluded to as temporarily sucking away its watery constituents, namely:

- (a) Watery diarrhea, especially in cholera and other acute diseases accompanied by diarrhea;
- (b) Large and rapidly accumulating serous effusions (slow accumulations would give time for the blood to take up water from the tissues and make up for its loss);
  - (c) Profuse sweats;
  - (d) Persistent vomiting or starvation of liquids (see Table II.);
  - (e) Increased blood pressure (exercise, massage, electricity).

Blood already lacking in red cells, if suddenly concentrated by such a loss of fluid, might deceive us into supposing it normal, because the number of cells in a cubic millimetre might be normal. In the presence, therefore, of any such reason for concentration of the blood, we should always modify our ordinary methods of inference from the blood count. For example, v. Limbeck records a case of hepatic cirrhosis with ascites, in which before tapping the ascites the count of red cells was 3,280,000 per cubic millimetre. Within twenty-four hours after tapping there were 5,160,000 cells per cubic millimetre, the reaccumulation of the ascitic fluid going on so fast that the blood was unable to adjust itself and became overconcentrated. A careless observation might have inferred a great gain in the corpuscular richness of the whole blood, when in fact not a corpuscle had been gained and those present had probably grown poorer in albumin.

η	CARLE	II -	-STARVATION.

Case.	Age.	Red cells.	White cells.	Hæmo- globin.	Remarks.
1 2	23 2	12,000,000 8,780,000			Stowaway. Ten days without food. Two weeks' starvation after caustic potash stricture of gullet.

It remains to speak of two other conditions in which what appears to be a true polycythæmia is found:

- 1. In persons living at high altitudes;
- 2. In persons suffering from phosphorus or CO poisoning.

#### 1. The Blood in High Altitudes.

The polycythæmia of those living at high altitudes increases the higher ones goes. Köppe¹ gives the following table:

Place.	Height above sea level.	Red cells.	Author.
Christiania	0	4,974,000	Laache.
Göttingen	148 metres	5, 225, 000	Schafer.
Tübingen	314 "	5, 322, 000	Reinert.
Zürich	414 "	5, 752, 000	Stierlin.
Auerbach	425 "	5,748,000	Köppe.
Reiboldsgrün	700 "	5,900,000	. "
Arosa	1,800 "	7,000,000	Egger.
The Cordilleras	4,392 "	8,000,000	Viault.

This extraordinary change takes place within two weeks of the time of taking up residence in a high place, and independent of any change in diet or manner of living. The sick and the well are equally affected and animals show similar changes. The hæmoglobin is also considerably increased, although it lags somewhat behind the corpuscles.

The corpuscles are often deformed and undersized during the earlier weeks of the change; but their volume, as determined by the hæmatocrit, is not increased. These changes suggest that the immediate increase in the number of red cells is due to budding or division of the cells already present in the circulation.

Later the poikilocytes and microcytes vanish and the hæmoglo-

<sup>&</sup>lt;sup>1</sup> Münch, med. Woch., 1890, No. 41,

bin percentage rises so as to correspond with the increased count of red cells.

On returning to low-land, the blood returns within a short time to its normal condition.

Many explanations have been offered for this interesting phenomenon. If it were a true new production of corpuscles we should expect some signs of blood destruction (icterus, hæmoglobinuria) on returning to the sea level. But there are no such signs. On the other hand, if the polycythæmia were a simple result of concentration due to the dryness of the high air, one would expect that the blood would quickly adapt itself, as in other (temporary) concentrations, by taking up water from the tissues. But in fact it does not do so. The cause of the increase is still a mystery.

## 2. Phosphorus and CO Poisoning.

The polycythæmia of acute phosphorus poisoning may reach as high as 8,650,000. This may be partly explained by concentration due to the occurrence of vomiting, but in some cases the increase seems out of proportion to the amount of vomiting.

With illuminating-gas poisoning there is usually no vomiting to speak of, and the cause of the marked increase in the red cells is unknown. Von Limbeck in two cases of CO poisoning showed respectively 6,630,000 and 5,700,000 red cells. Münzer and Palma' record 5,700,000. The white cells are also increased (see page 363).

<sup>1</sup>Zeit. f. Heilk., vol. xv., p. 1.

### CHAPTER VII.

#### ANÆMIA AND HYDRÆMIA.

#### 1. Anæmia.

Definition.—A deficiency in corpuscle substance, i.e., a deficiency in red corpuscles, in hæmoglobin, or in both, with or without changes in the total volume of the blood.

It is important to bear in mind that the color of the skin is not a safe guide in judging whether a person is anæmic. Thus out of 100 cases shown to be anæmic by actual blood examination, Townsend <sup>2</sup> found a good color in the cheeks of 4 and a fair color in 7 others. Eighty-nine were pale. The color of the lips is but little better as a guide, as the following table from Townsend's article shows:

Table of Color in One Hundred Cases of Anamia.

	Pale.	Fair.	Good.
Nails Cheeks Tongue Lips Conjunctivæ	84 76	5 7 15 21 25.5	0 4 1.2 2.4 10.5

My own impression would be that the lips and conjunctivæ were better guides than they are shown to be in this table.

In examining the color of the nails, the fingers should be flexed, as full extension may partly cut off the circulation under the nails.

<sup>1</sup>This is a clinical definition and makes no attempt to go to the root of the matter. I have little doubt that chemical or other changes in the serum are the cause of the corpuscular changes, which only mirror the deeper disease. But these chemical changes are as yet so little understood that we have to judge of their presence chiefly by their effect on the corpuscles.

<sup>2</sup> Townsend: Boston Medical and Surgical Journal, May 28th, 1896.

A. K. Stone' and his assistants estimated the hæmoglobin of 189 female patients who looked anæmic, and found over 75 per cent of hæmoglobin in 89, or nearly one-half of them. For a woman a hæmoglobin percentage of 75 per cent or more means practically normal blood.<sup>2</sup>

The most striking example of the fallacy of judging of anæmia by the color of the skin and mucous membranes is in the so-called "tropical anæmia." Practically all persons belonging to white races who take up their residence in the tropics acquire after a time an extreme pallor of the skin and mucous membranes, and this appearance has usually received the title of "tropical anæmia." It turns out, however, from the careful studies of several different investigators, that the blood of such persons shows absolutely no anæmia or other variation from the normal. The appearance of the skin is probably due to the action of the extreme climate on the peripheral nerves and vessels. Tropical anæmia is a condition not of the blood, but of the skin and subcutaneous tissues.

Every one's experience includes a few persons who are perfectly well despite an almost bloodless condition of the skin.

On the other hand, anæmia may exist when there is a good color in the face.

We are to judge of anæmia, then, solely by the blood examination, and this judgment can be accurately made on the basis of the small fraction of a drop used for examination, *provided* always that our technique is good, and provided we make allowances for a considerable error whenever there is reason to suppose that any venous and capillary stasis is present, or that the blood is temporarily concentrated or diluted.

# Distinction between Primary and Secondary Anamia.

In one sense all anæmia is secondary. It is due to some cause, a symptom in a chain of events. But in some cases we know the cause and in some we do not.

(a) Primary anæmia is that in which the causal factors are either entirely unknown or are apparently insufficient to produce so severe a disease. This division, like most of our statements about the blood,

<sup>1</sup> Boston Medical and Surgical Journal, August 23d, 1894.

<sup>&</sup>lt;sup>2</sup> When the hæmoglobin is high the number of corpuscles is never considerably diminished.

<sup>&</sup>lt;sup>3</sup> So far as present methods of examination go.

is a rough-and-ready one, held to provisionally until a better classification is discovered. It has a certain utility if not used with any less simple meaning than that given above.

There is no good evidence that there are any primary diseases of the blood-making functions. A case of secondary anæmia is one in which we have an obvious cause such as hemorrhage or malaria for the loss of corpuscle substance. Remove the cause and the anæmia ceases. Sometimes, however, after removal of the cause, e.g., after cure of a case of syphilis, the anæmia set agoing by the syphilis persists. On the other hand, there are few patients with "primary" anæmia who cannot recall some event in their past lives sufficient to account for a certain grade of anamia (e.g., a nervous shock, a hemorrhage, an attack of tertian malaria). if the anæmia that occurs after so slight a cause is of the pernicious or fatal type, we may fairly call it "primary." By this we mean that though the "cause" assigned might produce some anæmia, it was not sufficient to produce this fatal anemia and has presumably little or no connection with it. "Primary" means not the absence of any cause of anæmia in the history, but the absence of any sufficient cause so far as is known.

An attack of tertian malaria or a history of bleeding piles does not cause fatal anæmia in 999 out of 1,000 people who have such a history. In the 1,000th it is a case of post hoc and not propter hoc. Given the unknown cause that does lead to "primary" anæmia, and it might be that a pregnancy, a nervous shock, or the presence of intestinal parasites would act as the straw that breaks the camel's back; but the important causal factor is the unknown factor. Evidence is accumulating in support of Hunter's view that pernicious anæmia is due to excessive blood destruction produced by toxic substances absorbed from the gastro-intestinal tract. Chlorosis is now generally believed to be a disease representing defective blood-formation. But we are still in the realm of theory in these matters.

It is true that in the majority of cases we can tell from the blood examination alone whether a case is without known cause (= "primary") or symptomatic (= "secondary"). But there appear to be enough exceptions to this rule to make us cautious about stating it as a law.

it as a law. 
$$\text{An}_{\text{$\mathbb{Z}$MIA}$} = \left\{ \begin{array}{l} \text{Primary} = \left\{ \begin{array}{l} \text{Chlorosis.} \\ \text{Pernicious anamia.} \end{array} \right. \left\{ \begin{array}{l} \text{To be discussed under Special Pathology of the Blood,} \\ \text{Chapter VII.} \end{array} \right.$$

## Secondary Anamia.

- I. First Stage.—I defined an amia above as a diminution in corpuscle substance. In the milder types of this condition the number of red corpuscles is not diminished at all, but the individual cell is small, pale, and of light weight, through loss of nitrogenous matter. This is appreciated:
  - (a) As a lack of coloring matter;
  - (b) As a lowering of the specific gravity.

In the mildest grades of secondary anæmia there are no further changes. Such cases are those due to errors in hygiene—bad air, poor food, lack of light or exercise—to small hemorrhages, and to the earlier stages of the diseases next to be mentioned.

The lack of coloring matter is usually not present in every cell, as is seen in the stained specimens. Some are very pale at the centre, while others are well stained.

II. Second Stage.—Usually the next changes to appear are, like those already mentioned, qualitative, the number of red cells still remaining normal or approximately so.

The individual cell as seen in fresh preparations is more or less deformed and varies from its normal diameter, dwarfed forms usually being commoner than the giant forms. These variations in size and shape are sometimes termed "poikilocytosis," and the dwarf and giant forms are called respectively microcytes and macrocytes.

Maragliano¹ has included the above changes, together with others about to be described, under the heading of

Necrobiosis in the red corpuscles, attributing them to a pathological condition of the serum.

The changes united under this heading may be divided for convenience' sake into

- (a) Endoglobular changes.
- (b) Poikilocytosis and crenation.
- (c) Changes in staining properties.
- (d) Changes involving motility in the corpuscle as a whole, or in parts of it.
- (e) Decrease in the average diameter of corpuscles with loss of the power to form rouleaux.

All these changes may be watched in normal blood outside the <sup>1</sup> XI. Cong. f. Inn. Med., Leipzig, 1892.

vessels, as necrosis gradually comes on from contact with the air. Under pathological conditions the same changes may occur outside the body, but more quickly than usual (as other diseased tissues decompose more quickly after death than those of a sound man suddenly killed), or inside the body.

(a) Endoglobular Changes (see Fig. 26, a).—These consist in the appearance of clear hyaline spaces of various shapes within the

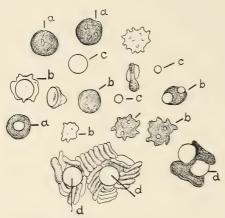


Fig. 26.—Degenerative Changes in Red Cells.

corpuscle, round, triangular, rod-shaped, etc. In the fresh specimen they change their shape rapidly and continually; in dried and stained specimens they appear as sharply outlined light spaces in the corpuscle. In normal blood these changes occur after thirty to seventy minutes outside the vessels. In some pathological conditions specimens show them the instant the blood is collected,

and presumably they were present before it left the vessels.

- (b) Crenation and Poikilocytosis (Fig. 26, b).—What we know as crenation in the corpuscles is probably the same sort of process which, occurring within the vessels, we call poikilocytosis. A lump rises at one or more points in the corpuscle, becomes more pointed, and gradually the whole cell acquires amæboid motions, assuming in succession the various shapes with which we are familiar in poikilocytes. Hayem has minutely described four types of motion in the red cells of anæmic blood.
  - 1. General amœboid motion of the whole cell.
  - 2. Vermicular motion of flagella-like prolongations.
  - 3. Oscillating motions, especially in small light cells.
  - 4. Pseudo-parasitic motion.
- (c) The pointed projections may break off and move about actively in the plasma. These motions, as well as the preceding amoeboid movement of the whole corpuscle, are to be explained as irregular contractions of the necrobiotic protoplasm, similar in a general way to the actions of a hen after its head is cut off. These

motions are not to be confounded with the finer Brownian or "molecular" movement to be seen in any healthy cell. The small bits broken off (Fig. 26, c) are doubtless the dwarf cells seen in dried and stained preparations. Curiously enough, these fragments tend again to assume the biconcavity characteristic of normal cells, as a drop of fat breaks into smaller but similar drops.

(d) Oval shape.—A great many cases of pernicious anæmia and

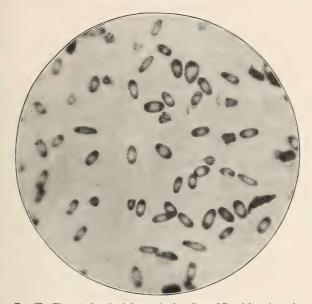


Fig. 27.—Elongated or Oval Corpuscles in a Case of Pernicious Anæmia.

some other diseases (see Epidemic Dropsy, page 256) show a marked tendency to oval shapes in corpuscles not otherwise considerably deformed. Even in normal blood I think there are a small number of oval forms, and in anæmia this number may be greatly increased till, as in Fig. 27, we get all the cells elongated. The same appearance can be produced by roughness in spreading the blood, but in such case the deformed corpuscles all point one way.

(e) Changes in Staining Properties.—Normal red corpuscles have affinity chiefly for acid stains. The same degenerative changes that lead to the alterations in shape and size above described alter the staining properties of the cell as well, so that it takes up two or three colors (according to the number present in the stain), either

as a diffuse mixture or irregularly, some parts of the cell taking color differently from others. In lead poisoning minute bits of the red cells become basophilic, so that the cell presents, with appropriate staining, a stippled look. The same change occurs in pernicious anæmia and occasionally in other varieties of anæmia. This has been termed a "polychromatophilic" or degenerative change. Some observers have supposed it to be rather of the nature of regeneration, believing that the cells take color in this unorthodox way because they are half-developed.

- (f) In many secondary anemias, especially in those associated with inflammations, the average diameter of the cells is lessened, and the rouleaux are not formed.
- (g) Cells may lose their hæmoglobin altogether, leaving only the shell of the corpuscle behind (see Fig. 26, d).

Now all these necrobiotic changes are characteristic of the severer grades of secondary anæmia such as occur in cancerous cachexia, phthisis, nephritis, etc.

In pernicious anæmia they are, as a rule, much more marked than in any other disease. Maragliano considers these degenerative changes to be due to toxic plasma. A lessened resistance to the ordinary plasma-environment on the part of the red cells would also explain them, and in such affections as paroxysmal hæmoglobinuria it seems the most probable cause. In syphilis the abnormal sensitiveness of the red cells to the influence of mercury seems another instance in which the red cells are immature, decrepit, or weak. In syphilitic children, for instance, mercury easily gives anæmia, while in healthy children it does not. This will be discussed more fully under syphilis.

The necrobiotic phenomena above described have been observed by Maragliano in carcinoma, lead poisoning, leukæmia, pernicious anæmia, purpura, eirrhotic liver, nephritis, pneumonia, malaria, typhoid, erysipelas, and tuberculosis. Celli and Guarnieri (Fortschritte der Medicin, 1889, No. 14) found them in measles and scarlet fever. Weintraub (Virchow's Archiv, vol. exxxi.) noted them in epilepsy, pyæmia, and catarrhal jaundice.

A decreased resistance to pressure, to electric currents and other influences has also been noted by v. Limbeck in some cases.

Such weakening of the red cells experimentally produced in ani-

<sup>1</sup>But in the severest forms of anæmia the diameters are apt to be increased (see below, Pernicious Anæmia).

mals by poisons has been found (Mya and Sanarelli, Arch. ital. di Biolog., xvii., 1892) to increase the susceptibility to infectious diseases.

III. Third Stage.—Here the number as well as the quality of the red cells begins to suffer. So far I have mentioned only the qualitative changes in secondary anemia and have purposely made these changes more prominent than the actual diminution in the count of red cells, because it is only comparatively rarely and in very marked cases that the diminution in red corpuscles is considerable. The blood characteristic of most cases of secondary anemia is one in which the number of red cells is approximately normal.

The important exceptions to this rule are: 1. The anæmias of infancy and early childhood. 2. Large hemorrhages (soon after their occurrence). 3. Malaria. 4. Acute septicæmia.

The direct and rapid destruction of the corpuscles by the malarial organism or hemorrhage account for this. Of sepsis and the anæmias of infancy I shall speak later.

IV. Fourth Stage.—The blood of secondary anæmia shows often evidence not only of degeneration and destruction of the cells but also of regenerative changes, namely:

#### Nucleated Red Cells.

These are usually divided into three groups

- (a) Normoblasts.
- (b) Megaloblasts.
- (c) Microblasts.

#### Normoblasts.

(a) The first are normally present in moderate number in the bone marrow of healthy persons, and in great numbers in the marrow after hemorrhage. They are generally considered to be a younger stage in the life of the corpuscle than the non-nucleated forms seen in the circulating blood. Hence the appearance in the peripheral circulation of this form of nucleated cell is considered to mean that, in the comparatively plentiful reproduction of red cells called forth in the marrow by the anæmia, a certain number of red cells leave the nursery (the marrow) before they are grown up and

circulate for a time in their immature state. A normoblast, then, represents an immature red corpuscle (see Plate IV.).

In size and color it is like an ordinary red cell except that we find, usually somewhat to one side of it, a round nucleus about one-half the diameter of the whole cell. With Ehrlich's tricolor mixture, this nucleus stains very deep blue, nearly black, and is sharply outlined against the pale yellow of the cell body around it.

The cell often looks as if it were pushing its nucleus out, *i.e.*, in many instances we see the nucleus projecting over the edge of the corpuscle, or half out of it, and occasionally we find it lying beside the corpuscle from which it has just emerged; but this appearance is probably an artifact and not, as Ehrlich thought, the regular way of disposing of the normoblast nucleus.

Very frequently the nucleus has toward the centre a light spot, sometimes so brilliant that it looks like the reflection of light from the surface of a drop of ink or any dark liquid, what artists call the "high light." Occasionally there are several of these light spots in a nucleus, or it may be all light blue-gray except a dark blue rim. This is the commonest type of normoblast. But now and then we meet with one when the nucleus is more or less separated into two or more pieces. These pieces are usually connected by pale-staining "bridges," perhaps radiating from a centre so that the nucleus is "rosette-shaped," or it may take any one of a large number of different shapes. The parts of the nucleus which are nearest the periphery of the cell usually stain more deeply than the "bridges" which join them.

Sometimes the nucleus breaks apart completely and we find two or more separate unconnected nuclei within the single cell. Or one of the pieces may be outside the cell and the others inside.

Rarest of all is the appearance of true mitosis in the nucleus of a normoblast.

# Megaloblasts.

(b) The typical megaloblast as usually described is so unlike the normoblast that we should not naturally think of them as near relations.

It does not occur anywhere in the healthy adult body, not even in the bone marrow. In the early feetal marrow and in the marrow

<sup>1</sup>Apparently the nucleus is absorbed or degenerates (see Israel and Pappenheim: Virchow's Archiv, vol. exliii.).

and circulating blood of grave forms of anæmia it is to be found, usually in company with a certain number of normoblasts.

Ehrlich described megaloblasts as the sign or product of a different type of blood formation, namely, the fætal type, and considered those anæmias in which it occurs as tending to a return of the blood to the feetal state. [This has been recently confirmed by the researches of Pappenheim, though Ehrlich's detailed theory of two methods of blood formation is now generally discredited. All nucleated red cells lose their nuclei by "absorption"; none by extrusion.] Ehrlich regarded the presence of megaloblasts as a bad prognostic sign, and believed that a pernicious or fatal anæmia was characterized by an excess of these cells over the normoblasts. recognized that they might be found in various milder forms of anæmia; but here the prevailing type is the normoblast, and regeneration may be more active than degeneration. In his general conception of the prognostic import of megaloblasts Ehrlich has been supported by the weight of later clinical observation, although it has been shown that the anæmia due to intestinal parasites can be cured, despite the presence of the megaloblasts as the prevailing type of nucleated red So far as I know this is the only exception to Ehrlich's cells. rule.

The typical megaloblast is an abnormally large cell (11 to 20  $\mu$  in diameter, frequently showing marks of degeneration (polychromatophilia) in its protoplasm, which is therefore brownish or purplish with the Ehrlich-Biondi stain. Its nucleus is very large, filling most of the cell, and contrasts with the normoblast nucleus not only by its greater size but by the pale, even stain which it takes up. The commonest color of the nucleus with the Ehrlich-Biondi stain is pale green or robin's-egg color. It is not stained evenly but dotted over with purplish granules arranged in a fine mesh like the knots in a fish-net (see Plate IV.).

Outside the nucleus there is usually a retraction band of clear white, apparently an empty space, separating the nucleus from the encircling protoplasm. The protoplasm close round this colorless ring is usually stained more deeply than the rest of the cell. Cracks and "flaws" are sometimes to be seen in the protoplasm, giving evidence, as its purplish stain does, of the necrobiotic changes described by Maragliano.

The outline of the whole may be quite circular: oftener it is oval or somewhat irregular, but rarely much deformed.

#### Microblasts.

(c) Microblasts, which are rarer than either of the varieties just described, consist of a nucleus like that of a normoblast or smaller, and contained in a cell body smaller than the normal red corpuscle. In the writer's experience the cell body is usually reduced to a few shreds of discolored protoplasm hanging about the nucleus (see Plate IV.). Their clinical significance is generally supposed to be that of megaloblasts.

# "Atypical Forms."

Often we find in a given specimen of blood only typical normoblasts, microblasts, or megaloblasts, and accordingly can easily reckon up the number of each kind and see which type of blood formation predominates. But sometimes there are cells present, about the classification of which we cannot come to a decision, and I have occasionally seen a specimen of blood containing a large number of nucleated red cells no one of which could strictly be classed either as a "normoblast," a "megaloblast," or a "microblast," as these are defined above.

The researches of Pappenheim have thrown much light on this difficulty. While insisting with Ehrlich that the megaloblast and the normoblast represent respectively the early feetal and the postuterine types of blood formation, and that there are no real "transitions" from the one to the other, he yet recognizes that the two varieties are not absolutely to be differentiated by any of the ordinarily accepted criteria such as size, color of nucleus, etc. Most "megaloblasts," he admits, are larger than most normoblasts, but there are occasional giant normoblasts and dwarf megaloblasts which by size alone are indistinguishable. The large, pale, delicately netted nucleus of the "megaloblasts" is simply a young nucleus. All young nuclei are relatively large and pale, while the small dark nucleus of the normoblast is simply an old or degenerating nucleus. The real criteria of the two varieties, according to Pappenheim, is not the size or color of nucleus nor of the whole cell, but the structure of the nuclear network. This is a point difficult to make out by ordinary staining methods and not easily appreciated. Luckily for us, most "megaloblasts" are larger than most "normoblasts"; and further, most of them as seen in the blood are young (i.e., have large pale nuclei with delicate chromatin network),

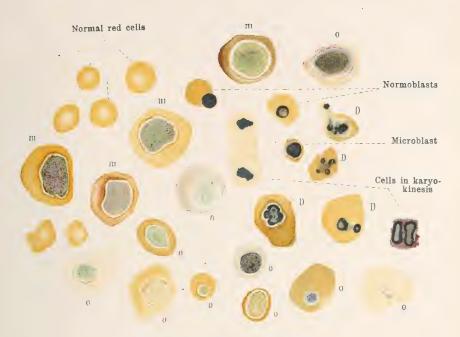


#### PLATE IV.

- (1) m,m,m,m—Young megaloblasts.
- (2) D,D,D,D; the *upper two* are probably *old normoblasts* with degenerating nuclei, and the lower two old megaloblasts with nuclei in a similar condition.
- (3) o,o,o,o, etc.—The two cells in the lower right-hand corner are probably old megaloblasts whose nuclei are nearly absorbed. The three cells immediately to the left of these are probably young normoblasts—the lowest one being the youngest. The other four cells marked "o,o,o,o" (those to the extreme left) are probably middle-aged megaloblasts. The two labelled "Normoblasts" are really old normoblasts. The appearance of extrusion of the nucleus on one of them is probably an artifact. The large cell on the extreme upper right-hand corner is probably a megaloblast with a "pyknotic" or ædematous (degenerating) nucleus.
- (4) In the young or "typical" megaloblasts (m,m,m,m) note the white line around the nucleus, the variations in its tint, and, in two of them, the discolorations of the protoplasm (polychromatophilia), especially near the nucleus. The lower of the two cells in karyokinesis shows the best.
  - (5) In the microblast note the ragged edge of the protoplasm.
- (6) In the lower portion of the plate ("cells deformed in size or shape") an actual field from a case of pernicious anæmia was copied. Macrocytes (or large cells), microcytes (or small cells), and misshapen cells or politilocytes are shown.
- (7) The "polychromatophilic cells" in the lower right-hand corner were stained with the same mixture as those to the left of them, but have taken up other colors besides the orange G, which alone is taken up by normal red cells.

## Examination of the Blood.

PLATE IV.



## Varieties of Nucleated Red Cells.

m. m. m. m. = Typical megaloblasts. D. D. D. D. = Cells with dividing nuclei. o. o. o. o. o. o. o. o. = Other (unnamed) varieties of nucleated red corpuscles.



Cells deformed in size or shape.



while most "normoblasts" are old, as shown by their small, dark, coarse-skeined nucleus, so that in the majority of cases Ehrlich's criteria for the two varieties are sufficiently correct for diagnostic purposes. Pappenheim of course wishes to abandon the terms "megaloblast" and "normoblast" altogether, but since size still remains the most easily recognized criterion of "megaloblasts" and "normoblasts" I shall continue to use the terms. On the chances, then, any nucleated red cell over 10 µ diameter should be classed as a megaloblast whatever the appearance of its nucleus, and any nucleated red cell under 10 µ diameter is probably a normoblast whatever the appearance of its nucleus. Microblasts simply represent degenerating forms (usually normoblasts) whose protoplasm is falling away. The clinical significance of the two varieties is just such as Ehrlich supposed. [These points will be made clearer by reference to Plate IV. and the remarks intended to explain it.]

In most cases of severe secondary anamia we find a few normoblasts. In very severe forms, whatever the cause, we may or may not find an occasional megaloblast. But these are much rarer than the normoblasts, even in the severest types of secondary anamia. The only exceptions to this rule are the anamias due to intestinal parasites, in which, though secondary and curable, the megaloblasts in some cases predominate over the normoblasts.

Summing up the changes characteristic of secondary anæmia, which includes almost all the important pathological appearances occurring in red cells, we have:

- $\text{I.} \left. \left\{ \begin{matrix} (a) \text{ Lack of hæmoglobin.} \\ (b) \text{ Lowered specific} \\ \text{ gravity.} \end{matrix} \right\} \text{ Characteristic of mild cases.}$
- II. The above and necrobiotic Characteristic of moderate changes of Maragliano.
- III.  $\begin{cases}
  (a) \text{ Lack of red cells.} \\
  (b) \text{ Presence of normolulates and the above cases.}
  \end{cases}$ Characteristic of severe cases.
- IV. Megaloblasts and the above Characteristic of very se-(I., II., and III.). vere cases.

The changes in the white cells will be discussed in the next chapter.

Among the commonest causes of secondary anæmia are: I. Infective and febrile diseases, acute or chronic. II. Malignant dis-

ease. III. Chronic suppurations, nephritis, chronic dysentery, cirrhosis of the liver. IV. Bad hygiene, pregnancy, and lactation. V. Intestinal parasites. VI. Poisons (lead, arsenic, etc.).

To discuss the way in which each of these influences acts in producing anæmia is tempting, but falls outside the plan of this book.

The following are good examples of the condition of the blood:

#### SECONDARY ANÆMIA.

			TTTT 24 .	77	
No.	Age.	Red cells.	White cells.	Hæmo- globin.	Remarks.
1	23	1,656,000	2,300 2,600	18	Post malarial.
		2,048,000	2,600	24	Seven days' treatment.
		1,808,000	3,200	30	Fourteen days' treatment.
		1,568,000	1.300	58	Twenty-four days' treatment,
		4,248,000	2,300	60	Thirty-four days' treatment.
6)	99	1,540,000	2,300 2,200		Malaria and dysentery.
3	22	1,984,000	6,700		
4	91	1,352,000	3,300		46 46
5	21 24	1,248,000	6,000		46 46
6	23	1,931,000	8,600	35	Æstivo-autumnal malaria.
0	70	1,001,000	0,000	00	Polynuclears, 73: lymphocytes, 24; eosinophiles, 3 megaloblasts = 1; normoblasts, 4.
7	35	3,070,000	2,100	35	Tertian malaria. Boston.
- 8	29	1,228,000	25,100	9	Tubal pregnancy, hemorrhage. Polynuclears, 92
	20	1,220,000	NO,100		lymphocytes, 7; eosinophiles, 1; normoblasts = 6 megaloblasts = 2.
9	50	1,960,000	13,400	22	Fibroid bleeding. Polynuclears, 85; lymphocytes, 14 eosinophiles, 1.
10	64	1,824,000	4,800	25 10	Hæmaturia.
11	25	1,448,000	3,600	10	Portal thrombosis, profuse hæmatemesis. Polynuclears 79; lymphocytes, 19; eosinophiles, 2; normoblasts =
		906,000		6	3; megaloblasts = 1.
10	-00		20,000	-0	Ten days later. Death next day. Autopsy.
12	39	3,200,000	20,000	52	Hepatic cirrhosis. Hæmoptysis yesterday.
13	46	2,992,000	13,800	20	Metrorrhagia.
14	31	2,500,000	7,500	30	Chronic diffuse nephritis.
15	40	2,040,000	9,600	10	Chronic dysentery. Polynuclears, 66.3; myelocytes, 1.4 normoblasts = 8; megaloblasts = 5. (Four hundred cells counted.)
16	53	4,030,000	12,700	23	Mitral stenosis. Skin lemon-yellow. Autopsy. Poly nuclears, 82; lymphocytes, 18; eosinophiles, 0; me galoblasts = 4; normoblasts = 22. (Four hundred cells counted.)
17	33	2,999,000	9.200	35	Chronic arthritis with ankylosis.
18	39	3,584,000	9,200 12,000	45	Alcoholic neuritis.
19	30	3,496,000	11,000	25	Chronic gastric catarrh.
20	42	3,020,000	11,600	25 50	Tertiary syphilis.
21	25	3,712,000	10,200	40	Ovarian cyst.
99	11	4,240,000	11,600	45	Friedreich's ataxia.
22 23	9	4,270,000	9,200	35	Cervical Pott's.
24	58	2,744,000	4,000	60	Autopsy. No cause found.
25	59	2,444,000	4,700	38	Polynuclear 73: lymphocytes 25: eosinophiles 2: nor
26	43	1,468,000	8,700	12	moblasts = 2; megaloblasts = 0.  Polynuclears, 71; lymphocytes, 27.8; eosinophiles, 1  myelocytes, 2; normoblasts = 7; megaloblasts = 1  Autopsy, fibroma of jejunum (ulcerative colitis).
27	53	1,472,000	12,400	20	Duodenal ulcer. Polynuclears, 75; lymphocytes, 23.6 eosinophiles, 1.2; myelocytes, 2; normoblasts = 1.
		1,876,000		19	Seventh day.
		2,148,000		17	Fourteenth day.
		2,440,000		21 23	Twenty-first day,
		3,196,000		23	Twenty-eighth day.
		2,774,000	6,600	28	Thirty-fifth day.
				28 23	Forty-third day. Polynuclears, 72.8; lymphocytes, 25 eosinophiles, 2; mast cells, 2; normoblasts = 1.
		2,820,000		30	Fiftieth day.
		3,440,000		43	Fifty-seventh day.
		3,832,000		46	Sixty-fourth day.
				48	

#### 2. Hydræmia.

- (a) Seen from the opposite point of view almost all cases of anæmia are hydræmic. That is, if the total volume of blood is to remain approximately constant (as it appears to do), any loss of solids (corpuscle substance) must be made up by water taken in from the tissues. Hence any anæmic person's blood is thin, watery, or hydræmic. Women's blood is somewhat more hydræmic than men's, because less rich in cells. Ordinary chlorosis and secondary anæmia show no more water than normal in the serum, but the cells are probably somewhat water-logged.
- (b) In many conditions of dropsy, whether from heart or kidney, we may have more water than normal, both in the plasma and in the corpuscles themselves, which are capable of taking up considerably more than their normal amount of water.
- (c) Any temporary dilution of the blood under the conditions mentioned above (ingestion of liquid, lowered blood pressure, etc.), is from one point of view a hydræmic condition.

No special clinical significance attaches to it other than that of anæmia, whose correlative it is.

(d) The investigations of Haldane and Smith seem to show that the total *volume* of plasma is greatly increased in certain types of anæmia, although its specific gravity remains normal. This is one type of hydræmia (see page 6).

## CHAPTER VIII.

# LEUCOCYTOSIS — LYMPHOCYTOSIS — EOSINOPHILIA — MYELOCYTES.

Much confusion has been caused in the past by the failure to see in leukæmic blood anything more than an extreme and permanent form of leucocytosis, while leucocytosis was thought of as a mild and temporary leukæmia.

We know now that they are quite different phenomena, differing not in the number, but in the *kind* of cells present in the increased numbers.

## Definition.

There are many difficulties in defining leucocytosis. To my mind the term is best used to mean: An increase in the number of leucocytes in the peripheral blood over the number normal in the individual case, this increase never involving a diminution in the polymorphonuclear varieties, but generally a marked absolute and relative gain over the number previously present.

(a) I say "in the peripheral blood" because most observers now hold that leucocytosis is not always a real increase in the total number of leucocytes in the body, but is often the result of chemotaxis or thermotaxis, the cells being drawn or attracted to the periphery and out of the internal organs. At any rate, in the blood drop which we draw (whether also in the internal organs or not), the leucocytes are present in increased numbers per cubic millimetre. The studies of Muir, Ehrlich, and others have made it clear that there are two types of leucocytosis. (1) The first includes only leucocytoses of sudden appearance and short duration such as those produced by cold baths. Here there is no time for the production of new cells and the increase of white corpuscles in the peripheral blood corresponds in all probability to a decrease in the number ordinarily hoarded in the pulmonary capillaries and elsewhere, the total number of leucocytes in the body remaining approximately the

- same. (2) When leucocytosis lasts for months, as is often the case in long-standing suppurations and malignant neoplasms, there is no doubt that leucocytes are formed and turned into the circulation more rapidly than under normal conditions. The total number of leucocytes in the body is then greatly increased. In such cases the marrow is found to be hyperplastic whether the leucocytosis is due to bacterial toxins (Ribbert) or to long-continued experimental injections of albumoses (Taylor). Chronic leucocytosis, then, is a function of the marrow.
- (b) In persons not usually to be considered sick, but simply somewhat wizened or ill-nourished, the normal count of white cells may be as low as three thousand per cubic millimetre. For such an individual ten thousand cells per cubic millimetre would be a decidedly pathological condition. On the other hand, there are persons, usually those of notable vigor and good nutrition, whose white cells rarely fall below ten thousand.

Obviously we must take account of these differences both in our definition and in our practice if we are to reason correctly from the data of blood examination.

(c) Further we must lay stress upon the varieties of leucocytes whose increase constitutes leucocytosis in distinction from either variety of leukæmia (myeloid, or lymphatic).

For instance, given a count of eighty thousand leucocytes per cubic millimetre, we cannot tell without knowing the varieties of cells present whether the case is a genuine leukæmia or merely a leucocytosis symptomatic of pneumonia, suppuration, malignant disease, or other conditions.

(d) Thus defined leucocytosis is of two kinds. 1. That in which the relative proportions of the different varieties to each other is unchanged. 2. That in which the increase is made up solely or largely by a gain in the polymorphonuclear leucocytes.

The latter includes nearly all long-standing and pathological leucocytoses, the former being confined chiefly to the transient physiological leucocytoses next to be described.

(e) Lastly, in order to be sure that the polymorphonuclear cells are not decreased, we must know approximately what the normal percentage for that individual is. The normal percentage of these cells in infancy is from twenty-eight to forty per cent. In adults it is much higher, but varies like the total count, according to conditions of nutrition, etc. Thus the normal for adults is usually set

at from sixty to seventy per cent, and if we include the obviously ill-nourished, but not actually sick, and also those in blooming health, we shall have to widen our normal limits considerably. From fifty to seventy-five per cent are within normal limits according to the above conception. But obviously we can make no absolute judgment by a standard so vague. It is much better, I think, to consider each individual as his own standard within these limits, his count of polymorphonuclear cells being a fair measure of the soundness and vigor of his metabolism. Thus, in an obviously debilitated individual, we should consider seventy-two per cent of these cells very high, while in a vigorous athlete it might not be so.

It is the endeavor to include all these limiting conditions that has made my definition so long and involved. It gives us, if it turns out to be true, some better way of classing individuals than as "sick" or "well" as regards their blood state. We find out how well or how sick their blood is (to a certain extent), (a) by the total number of leucocytes present, and (b) by the proportion of polymorphonuclear neutrophiles in a given one thousand of these leucocytes. These data tell us approximately how normal or how abnormal a given individual's blood is. When a given disease like pneumonia occurs, we need to know, if possible, what is the ordinary leucocyte count and differential count of that case, on top of which a leucocytosis may (or may not) be built up.

Condition of stasis, temporary blood concentration, dilution, and vasomotor disturbances must, of course, be excluded or allowed for, since these may increase not only the total leucocyte count, but often the percentage of polymorphonuclear cells. Whether or not differences of race make any difference in the normal count of white cells, I cannot say, but certainly the average of a group of college athletes would be higher than that of some country towns in New England where everybody is more or less under-nourished; and if one is to practise among all sorts and conditions of men, I think he cannot but expect to find people's leucocytes vary all the way from 5,000 to 10,500 per cubic millimetre, without there being more than malnutrition to account for the lower figures.

We may divide leucocytoses for convenience' sake into: 1. Physiological leucocytoses. 2. Pathological leucocytoses.

#### Physiological Leucocytoses.

- 1. Leucocytosis of the new-born.
- 2. Leucocytosis of digestion.
- 3. Leucocytosis of pregnancy.
- 4. Leucocytosis post partum.
- 5. Leucocytosis after violent exercise, massage, and cold baths.
- 6. Leucocytosis of the moribund state.

# The Leucocytosis as Affected by Digestion.

(a) Total abstinence from food lowers the leucocyte count. In the blood of the professional faster Succi, the number sank within his first week's fast to 861 per cubic millimetre. After the first week it rose to 1,530, and remained there throughout his thirty days' abstinence (Luciani). The polymorphonuclear cells and eosinophiles are said by Tauszk to be increased in chronic starvation.

Von Limbeck counted the blood of a melancholic patient who had fasted a week, and found 2,800 white cells per cubic millimetre. These facts support the idea that the number of leucocytes depends (within certain limits) on the individual's assimilation of food. In cancer of the gullet we find similar low figures.

(b) After a meal rich in proteids the leucocyte count rises about thirty-three per cent in most sound persons. Ten thousand cells may perhaps be considered the average, three to four hours after a proteid meal, but if the count before a meal is only 4,000 or 5,000, digestion will perhaps not raise it above 7,000, while vigorous adults may show 13,000. Digestion leucocytosis is always relative to the count of the individual's blood when fasting. This is to be obtained preferably before breakfast, as during the day the leucocytosis caused by one meal may not be gone before the influence of the next meal begins. Examples of digestion leucocytosis in diseases other than gastric are seen in the following table:

Case.	Diagnosis.	Count before food.	Count after food.
2	Cirrhosis	7,500	18,900 21,700 13,500 8,650

 $<sup>^1\,^{\</sup>rm o}$  Das Hungern," German translation by O. Fränkel. Hamburg, 1890.  $^7$ 

Occasionally we see sound persons with little or no digestive leucocytosis. Some of these cases are to be explained by habitual constipation (v. Limbeck); in others the reason is more obscure. But there is no doubt of its being the rule after meals of mixed or proteid diet.

Any disease of the gastro-intestinal tract, whether functional or organic, may prevent the appearance of the digestion leucocytosis (see later under Diseases of the stomach, page 293). In anæmic and debilitated conditions it is frequently absent.

In children it is especially marked. Schiff records a case of a healthy infant whose blood an hour after birth showed 19,500 (see next section), after its first meal 27,625, and after its fourth meal 36,000 white cells per cubic millimetre. After the second day this gradually diminished.

Food seems to call forth a greater leucocytosis in proportion as it is a *novelty* in the stomach. Patients with gastric ulcer who had been fed exclusively by rectum for some weeks show a greater leucocytosis after their first meal than later. Perhaps the size of the digestion leucocytosis in the new-born is to be similarly explained. In diabetics the digestion leucocytosis is sometimes very large.

The leucocytosis can usually be observed one hour after a meal, increases for two, three, or even five hours according to the slowness of digestion, then falls again.

Burian and Schur<sup>2</sup> found an increase of the polymorphonuclear varieties in those cases in which an increase of the total count took place at all. Rieder reports a lymphocytosis. It is probable that both lymphocytes and neutrophiles are increased, while eosinophiles are reduced.

# Diagnostic Value.

1. When we wish to know whether a person is accurate in such statements as that they have "eaten nothing for a week," we can get evidence from the leucocyte count, which should be very low if the assertion be true. Whenever we cannot communicate with a patient and wish to know how much food he has taken of late, we can form some idea from the blood examination. In the case of a patient who spoke only Russian, I was led to look for a stenosis of the gullet by the lowness of the leucocyte count (2,700), and the probang confirmed the suspicion.

<sup>&</sup>lt;sup>1</sup> Zeit. f. Heilk., xi., 1890.

<sup>&</sup>lt;sup>2</sup> Wien. klin. Woch., February 11th, 1897.

- 2. As suggested above, we can form some idea of a person's general vigor, nutrition, and capacity to assimilate food by the number of leucocytes and the proportion of mononuclear cells, as compared with the average figures for that age and locality. Persons debilitated from any reason are apt to show it in their blood by the changes above mentioned, the element of hysteria being sometimes recognizable by other signs (see below "Eosinophilia," page 115).
- 3. Slowness of digestion is indicated by a late appearance of the digestion leucocytosis. The inferences to be drawn from the blood in diseases of the gastro-intestinal tract will be discussed later (page 298).
- 4. Perhaps the chief importance of digestion leucocytosis is as a possible cause of false inferences, through being taken for a pathological increase. Bearing this in mind, we must always examine the blood as *near* a meal as possible, or better still before breakfast.

# Leucocytosis of the New-Born.

The following table is compiled from the best authorities on the subject (Schiff, Gundobin, Bayer, Hayem, and others):

Age.	Red cells.	Leucocytes.
At birth	5,900,000	17,000 to 21,000 (26, - 000 to 36,000 after first feeding).
End of first day	7,000,000 to 8,800,000	24,000
" second day	Generally increased.	30,000
" fourth day	6,000,000	20,000
" seventh day	5,000,000	15,000
Tenth day		10,000 to 14,000
Twelfth to eighteenth day		12,000
Sixth month		12,000
Sixth year and upward		7,500

The increase is explained by Lepine, v. Limbeck, and others as a combination of blood concentration with large digestion leucocytosis. Gundobin and others are opposed to this theory. Certainly the influence of digestion on infants' blood is much greater than in adults. After a meal 30,000 leucocytes is never a very high count in infants under two years.

A fuller discussion of the subject will be found in the chapter on the blood in infancy.

## The Leucocytosis of Pregnancy.

Most primiparæ show during the later months of pregnancy a moderate increase of all varieties of leucocytes. Thirteen thousand cells per cubic centimetre is about the average count.

In multiparæ it occurs in only about fifty per cent of the cases. Digestion leucocytosis "on top of" the constant pregnancy leucocytosis, so to speak, rarely occurs.

As mentioned above, the relative percentage of the different types of leucocyte remains unchanged, so that all varieties must be equally increased (eosinophiles excepted). The fact that digestion does not increase the pregnancy leucocytosis, leads to the suggestion that the whole thing may be only a prolonged digestion leucocytosis—the mother having to eat for two. The swelling of the breasts may also account for part of the leucocytosis. In the last weeks of pregnancy the leucocytosis increases till at the beginning of labor it is often 16,000 to 18,000. It has no diagnostic value, as it is not present during the earlier months of pregnancy when diagnosis is difficult, and in the later months such conditions as hydatidiform mole and fibroid tumors might raise the count of white cells as much as pregnancy.

# Leucocytosis After Parturition.

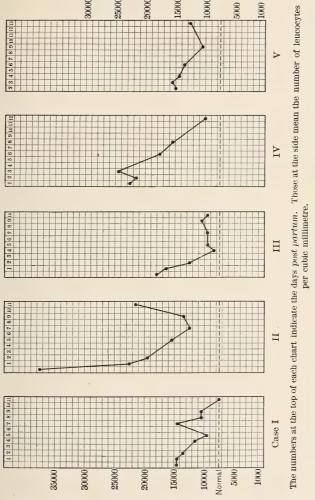
The following charts illustrate the course of the leucocyte curve from the time of parturition till the end of the second week after it.

All were primiparæ excepting Nos. 5, 8, and 9. There was no sepsis in any case, and the temperature charts were practically normal after the second day. No reasons are known for the variations between the different cases. All were counted at the same hour of the day, and under the same conditions of nutrition. All nursed their children.

The only importance of this leucocytosis is that it might be confounded with a pathological leucocytosis in a case suspected of being septic. Just how long the leucocytosis is prolonged during lactation has not been studied so far as I am aware, but it certainly may go on several weeks.

Violent exercise, massage, and short cold baths have been shown to cause a temporary increase in the number of leucocytes in the peripheral blood, all varieties of the cell being equally increased. The explanation usually given is that the blood is concentrated by vasomotor contraction and rise of blood pressure.

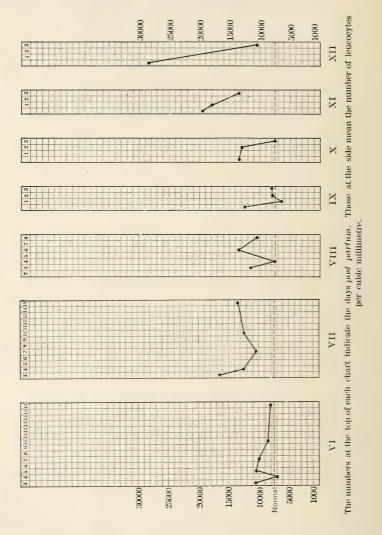
Schultz (Deut. Arch. f. klin. Med., 1893, page 234) found the leucocytosis of exercise amount to about the same as that of diges-



tion, 11,000 to 13,000. He also noted that in dogs merely opening the peritoneum aseptically or breaking a leg caused leucocytosis.<sup>1</sup>

<sup>&</sup>lt;sup>1</sup> Blake (Annals of Surgery, 1901) reports on the blood of runners in a recent "Marathon race" as follows: The leucocytes rose from 7,000 to 10,000 before the race to 18,000 to 21,000 after it. The polynuclear cells were increased and eosinophiles absent. After fractures Blake and Hubbard found no increase in leucocytes.

Thayer studied twenty cases of typhoid and found an average of 7,724 white cells before and 13,170 after a Brand bath (*Johns Hopkins Medical Bulletin*, April, 1893). The increase took place equally in all varieties. Winternitz (Imperio-Royal Medical So-



ciety, Vienna, February, 1893) came to a similar conclusion and found also that prolonged cold bathing decreased the number of white cells (dry cold does the same). A patient was recently

brought to the Massachusetts Hospital who had fallen through a hole in the ice and been some minutes in the icy water. His temperature was 91.8° by the rectum. Blood count showed 17,500 leucocytes per cubic millimetre. Next day he was perfectly well. On the contrary, short hot baths decrease and prolonged ones increase the number of leucocytes.

Local arm baths have a similar effect, raising the count of leucocytes in the blood of the immersed arm if cold and short, and lowering it if hot and short, while prolonged immersion has an opposite effect. In the other arm the counts go up when those of the immersed arm go down, and *vice versa* (Rovighi). Mitchell <sup>2</sup> found that the leucocytes showed distinct increase (as well as the red cells and hæmoglobin) after one hour's general massage.

All these forms of leucocytosis are usually explained by changes in blood pressure, and vasomotor changes affecting the calibre of the peripheral vessels and consequently their contents.

## Terminal Leucocytosis.

The leucocytosis of the moribund state, though by no means invariable, occurs in many cases, whether from the influence of a terminal infection or from stasis. When death is sudden or rapid it does not occur. It seems to be analogous to the terminal rise of temperature seen at the close of many chronic non-febrile affections. The longer the patient is moribund the higher the count reaches. In pernicious anæmia the increase may be so great as to simulate lymphatic leukæmia. Such a case occurred in the writer's own experience. The patient had presented the signs and symptoms of pernicious anæmia, and the blood was typical of the disease in all respects except for the lack of nucleated red cells.

Slides taken on the day of death showed a ratio of one white to fifteen red cells, the small lymphocytes greatly predominating, but the autopsy revealed simply the lesions of pernicious anæmia. The differential count of one thousand leucocytes on the day of death showed: Lymphocytes, 91.7 per cent; polymorphonuclear cells, 7.7 per cent; eosinophiles, 0.5 per cent. Four megaloblasts were seen while counting these. The total leucocyte count was unfortunately not made.

In ordinary cases the differential count shows an increase in the

<sup>&</sup>lt;sup>1</sup> Arch. Ital. d. Clin. Med., xxxii., 3, 1893.

<sup>&</sup>lt;sup>2</sup> American Journal of the Medical Sciences, May, 1894.

polymorphonuclear leucocytes. Thus in a case reported by Rieder, in which the leucocyte count rose during the last two days of life from 7,800 to 59,300, the polymorphonuclear cells constituted 87.5 per cent of the whole 59,300.

#### PATHOLOGICAL LEUCOCYTOSES.

For convenience' sake these may be divided as follows:

- 1. Post-hemorrhagic leucocytosis.
- 2. Inflammatory leucocytosis.
- 3. Toxic leucocytosis.
- 4. Leucocytosis in malignant disease.
- 5. Leucocytosis due to therapeutic and experimental influences.

## 1. Post-hemorrhagic Leucocytosis.

Within an hour after a large hemorrhage we find commonly a considerable increase (16,000–18,000). In hemorrhage from the stomach this disappears again usually within a day or two, while in ordinary traumatic hemorrhage it persists longer. This last fact may perhaps be explained, as v. Limbeck suggests, by the local conditions in the wound rather than by the loss of blood in itself.

The polymorphonuclear leucocytes are usually increased relatively and absolutely as in other forms of pathological leucocytosis. Sometimes we have lymphocytosis (see page 114). The average of increase in the white cells is parallel in a general way to the anæmia produced in the individual, *i.e.*, it depends on his powers of reeuperation rather than on the amount of blood lost. Its duration follows the same rule.

# 2. Inflammatory Leucocytosis.

I use the term "inflammatory leucocytosis" rather than "leucocytosis of infectious diseases" because there is a considerable number of infectious diseases in which no leucocytosis occurs, while it accompanies almost all forms and cases of inflammation. Nevertheless I shall class under this heading some diseases in which inflammation plays but a very subordinate rôle.

I. Although *purulent and gangrenous* processes usually cause a higher count of white cells than *serous* processes, the amount of the exudation is not a measure of the amount of leucocytosis. It

 $<sup>^{\</sup>scriptscriptstyle 1}\textsc{Further}$  account of the blood after hemorrhage will be found on p. 126 et seq.

seems to depend rather on the resultant of two forces, viz., the severity of the infection and the resisting power of the individual. These factors may interact in various ways:

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    Infection mild: resistance good = small leucocytosis.
    " less mild: " less good = moderate leucocytosis.
    " severe: " good = very marked leucocytosis.
    " poor = no leucocytosis.
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This will be illustrated later under "Pneumonia" and under "Sepsis." Experiments on animals show that whereas moderate-sized doses of septic cultures, not sufficient to kill the animal, are followed by leucocytosis, larger doses after which death follows speedily, do not raise the leucocyte count at all. Animals weakened by any cause show less leucocytosis to a moderate dose than strong animals.

If the individual reacts from the shock his leucocytes are increased again and rise above normal. If reaction fails the leucocytes do not rise.

- II. Inflammatory leucocytoses differ from physiological leucocytoses—
  - (a) In being usually of larger extent and greater duration.
- (b) In being almost always accompanied by a relative and absolute increase in the percentage of polymorphonuclear cells.
- III. The course of the leucocytosis as regards both amount and duration shows, like the temperature chart, certain more or less characteristic differences in different diseases.
- IV. In some cases in which the absolute number of leucocytes is not increased, we see a relative increase in the polymorphonuclear cells, pointing to the fact that influences are at work similar to those which produce an *absolute* increase.
- V. That the amount of exudation is not of itself a measure of the amount of leucocytosis is shown by the fact that erysipelas or scarlet fever may be accompanied by as high a count as the average count in pneumonia or empyema.

That purulent exudations usually have more effect on the white cells than do serous ones is due, I suppose, to the fact that a purulent inflammation usually means a severer infection.

VI. No direct connection exists between leucocytosis and fever, many febrile affections running their course with a normal leucocyte count. When both leucocytosis and fever are due to the same

causes they rise and fall together, but the correspondence is rarely accurate, and marked leucocytosis may exist without fever.

VII. Acute, rapidly spreading inflammations seem to produce a greater leucocytosis (other things being equal) than those in which the process is relatively chronic and stationary. For instance, an appendicitis, when well walled off and stationary, shows less increase in white blood cells than while its lesions are progressing. But peracute, overwhelming general sepsis may have no effect on the leucocytes, the reactive power of the organism being crushed.

VIII. Most inflammatory leucocytoses are preceded by a temporary diminution in the number of leucocytes. This occurs in animals from *shock* of any kind (blows on the head, tying to the etherizing board), and it seems not unlikely that the cause is the same in all cases.

The following is a list of the more important inflammatory or infectious conditions in which leucocytosis appears:

- 1. Infectious diseases with comparatively slight local inflammatory processes:
  - (a) Asiatic cholera.
  - (b) Relapsing fever.
  - (e) Typhus fever (according to the majority of observers).
  - (d) Scarlet fever.
  - (e) Diphtheria and follicular tonsillitis.
  - (f) Syphilis (secondary stage).
  - (g) Erysipelas.
  - (h) The bubonic plague.
  - (i) Yellow fever (some cases).
  - 2. Infectious diseases with more extensive local lesions:
  - (a) Pneumonia.
  - (b) Smallpox (suppurative stage).
- (r) Malignant endocarditis, puerperal septicæmia, and all pyæmic and septicæmic conditions.
  - (d) Actinomycosis.
  - (e) Trichinosis.
  - (f) Glanders.
  - (g) Acute multiple neuritis (febrile stages).
  - (h) Acute articular rheumatism.
  - (i) Septic meningitis and cerebro-spinal meningitis.
  - (j) Cholangitis, cholecystitis, and empyema of the gall bladder.

- (k) Acute pancreatitis.
- (l) Endometritis, cystitis (some acute cases).
- (m) Gonorrhea.
- 3. Local inflammatory processes:
- . (a) Abscesses of all kinds and situations, such as Felon.

Carbuncle, furunculosis.

Tonsillar and retropharyngeal abscess.

Appendicitis, phlebitis (some cases).

Pyonephrosis, perinephritic abscess, and pyelonephritis.

Osteomyelitis, empyema.

Psoas and hip abscess when not simply tuberculous.

Abscess of lung, liver, spleen, ovary, prostate.

Salpingitis and pelvic peritonitis, epididymitis.

(b) Inflammations of the serous membranes including:

Pericarditis, peritonitis, arthritis (serous or purulent, non-tuber-culous), conjunctivitis.

(c) Gangrenous inflammations, as of the

Appendix, lung, bowel, mouth (noma).

(d) Many inflammatory skin diseases, such as dermatitis, pemphigus, pellagra, herpes zoster, prurigo, some cases of universal eczema, etc.

# 3. Toxic Leucocytosis.

Under this heading I have grouped most of the conditions not obviously to be explained as infectious or inflammatory (though some may turn out to be such) and not due to malignant disease or therapeutic agencies. This classification is chiefly for convenience' sake and represents only a guess at the real explanation of the leucocytosis:

- (a) Leucocytosis of illuminating-gas poisoning.
- (b) " quinine poisoning.
- (c) " rickets (many cases).
- (d) " the uric-acid diathesis, gout.
- (e) " acute yellow atrophy of the liver.
- (f) " advanced cirrhosis of the liver (some cases), especially with jaundice.
- (g) " acute gastro-intestinal disorders (pto-maïns?).
- (h) " chronic nephritis, usually in uræmic cases.

- (i) Leucocytosis after injections of tuberculin and thyroid extract.
- (j) " after injection of normal salt solution (intravenous).
- (k) " after ingestion of salicylates, potassium chlorate, or phenacetin.
- (l) "during and after prolonged chloroform narcosis.

  Zerber (Inaug. Dissert., Berne, 1896) found the leucocytes increased after etherization in 96 out of 101 cases examined. The increase amounted in 35 cases to double and in 23 to triple the count before ether.

In no case was the count made after etherization and before the operation was begun, so that it is impossible to say how far the leucocytosis was due to ether. Since it has been shown that in animals a leucocytosis can be produced simply by opening the peritoneum, or even by the shock of tying the animal to the operating table, it is essential to rule out the effects of the operation itself.

In Chadbourne's careful study of 21 cases (*Phil. Med. Journ.*, February 18th, 1899) counts were made just before etherization and then after full narcosis, but before the operation was begun. Digestion leucocytosis was excluded. Every case showed an increase, the average gain being 37.3 per cent. The increase is exceedingly rapid, some cases showing a change of 70 per cent within a few minutes; it is most marked in the first part of etherization. The degree of leucocytosis did not seem to depend on the duration of narcosis.

Differential counts showed that all varieties of leucocytes were increased—the lymphocytes slightly more than the others.

Chadbourne considers the leucocytosis due to the irritation of the ether vapor upon the mucous membrane of the respiratory tract.

Blake and Hubbard in a study of 28 cases before and after full ether anæsthesia, found no considerable increase in the circulatory leucocytes (*Annals of Surgery*, 1901).

Possibly the leucocytosis of acute delirium belongs also in this group.

# 4. Leucocytosis of Malignant Disease.

Very likely this belongs more properly under one or another of the classes just mentioned. Some observers think that it occurs only from the inflammation excited in the periphery of some malignant tumors; others that it is due to absorption of morbid products from the tumor itself; others again that it is to be accounted for by the cachectic state associated with the growth of the tumors. The details and conditions of its occurrence will be discussed later (page 370).

## 5. Leucocytosis Due to Therapeutic and Experimental Influences.

Pohl<sup>1</sup> found that most of the so-called tonics and stomachies produce a slight increase in the white cells in animals, particularly the vegetable tonics like tineture of gentian, and oil of anise seed, while bismuth, bicarbonate of soda, and iron had no such effect. Quinine, caffeine, and ethyl alcohol gave likewise negative results. Von Limbeck found leucocytosis in men after oil of peppermint and oil of anise seed.

 ${
m Binz^2}$  got the same results with camphor. In all these experiments the substances were given by the mouth.

Using subcutaneous or intravenous injections, Löwit experimented on animals with hemialbumose, peptone, pepsin, nucleinic acid, nuclein, extract of blood-leech, pyocyanin, tuberculin, curare, uric acid, urate of sodium, and urea. All but the last of these produce temporary decrease followed by increase of leucocytes.

Goldschneider and Jacob <sup>3</sup> used extracts of various organs. Extract of spleen, marrow, and thymus produced leucocytosis preceded, as in Löwit's experiments, by a brief diminution in the number of leucocytes, while extract of pancreas, thyroid, kidney, and liver had no effect.

Winternitz<sup>4</sup> injected a large variety of substances subcutaneously and found that the degree of leucocytosis was parallel to the degree of local reaction excited.

For example, neutral salts and weak acids or alkalies produced slight local inflammation and a leucocytosis of from forty to seventy-five per cent of the original count. But irritants like turpentine, croton oil, nitrate of silver, sulphate of copper, mercury, antimony, digitoxin, etc., produced local suppuration (aseptic) and much greater leucocytosis (two hundred to three hundred per cent).

Pilocarpine and antipyrin have been found by von Jaksch and others to produce marked increase in the number of leucocytes when

<sup>&</sup>lt;sup>1</sup> Arch. f. exp. Path. u. Pharm., 1899, vol. xv.

<sup>&</sup>lt;sup>2</sup> Arch. f. exp. Path. u. Pharm., vol. v., p. 122.

<sup>&</sup>lt;sup>3</sup> Arch. f. Anat. u. Physiol., 1893, p. 567.

<sup>&</sup>lt;sup>4</sup> Arch. f. exp. Path. u. Pharm., vol. xxxv., p. 77.

given subcutaneously. During the use of thyroid extract Richter (Centralblatt f. inn. Med., 1896, p. 3) noted leucocytosis. Renzi and Boeri report leucocytosis (slight) after purgatives such as castor oil, podophyllin, and scammony.

A large number of observations on the effects of injections of bacteria or their toxins agree in the following results:

- 1. When the dose is very large the leucocytes are reduced, and the animal dies.
- 2. When the dose is not sufficient to kill the animal the temporary diminution in the leucocytes is soon followed by leucocytosis.
- 3. When the dose is slowly fatal the count of leucocytes oscillates up and down within wide limits.
- 4. Animals previously rendered immune to the poison injected show little or no leucocytosis.
- 5. Leucocytosis is more easily called forth and of greater extent in young animals.
- 6. Most pathogenic organisms act similarly, but bacilli and toxins of tuberculosis as a rule cause no leucocytosis.
- 7. There is no evidence that any one variety of leucocyte is attracted by any particular bacillus or toxin.

In the above sketch of therapeutic and experimental forms of leucocytosis no attempt has been made to give anything but the more interesting and important outlines of the immense amount of work done.

# Cell Structure of the Leucocytes in Leucocytosis.

Hitherto we have spoken as if leucocytosis meant only an increased *number* of the normal cells, but one cannot study the cell forms in extensive pathological leucocytosis without noting in many cases *qualitative* changes in the individual cells. These are chiefly:

- 1. A greater or less approximation of the nuclei of polymorphonuclear neutrophiles to the appearances of the myelocyte nucleus. As will be mentioned later under leukæmia, we find in every blood containing many myelocytes numerous cells whose nucleus is on the border-line between the myelocyte and the polymorphonuclear stage, so far as appearances go. Now in leucocytosis we find the same "border-line" cells in smaller numbers, the *likeness* to the myelocyte sometimes passing into *identity* in one to three per cent of the cells.
- 2. Türck's "Reizungsformen" or "stimulation-cells" in which the protoplasm of the cell (which is in other respects like a large

lymphocyte) shows a greater or less approximation to the appearance of myelocyte protoplasm, *i.e.*, a diffuse violet or purple color exactly as in the myelocyte but *non-granular*. Engel makes a separate variety of this cell, giving it the useless name of "mononuclear cell." Weil calls it the "non-granular myelocyte." Türck considers

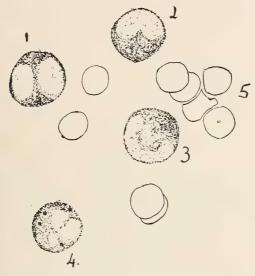


Fig. 28.—Atypical Leucocytes seen in Leucocytosis. 1, Leucocytes with polar arrangement of nuclei (mitosis?); 2 and 3, leucocytes with nuclei resembling those of myelocytes; 4, leucocyte containing two kinds of granules.

its presence in the circulating blood to indicate a *stimulation* of the marrow by the toxins of disease, resulting in the passage of this—supposedly immature—cell into the blood.

3. Other finer changes, such as the number, size, and staining power of the neutrophilic granulations, polar position of the nuclei, etc. (see Fig. 28), require further study.

Changes like the above militate against the idea that leucocytosis is simply a matter of the distribution of fully formed leucocytes in the peripheral or internal vessels.

For an account of iodophilia or the iodine reaction in the polynuclear leucocytes during suppurations see p. 239.

# Absence of Leucocytosis.

It is of fully as great a practical assistance to us to know that in certain infective diseases leucocytosis is regularly absent as to know

those conditions in which it is to be expected. Among the most important diseases in which leucocytosis is conspicuously absent are:

- (a) Typhoid fever.
- (b) Malaria.
- (c) Grippe (most cases).
- (d) Measles.
- (e) Rötheln and mumps.
- (f) Cystitis.
- (g) Tuberculosis, including—

Incipient phthisis.

Miliary tuberculosis.

Tuberculous peritonitis.

" ostitis and periostitis.

" pleurisy.

" pericarditis.1

In some of these affections, notably in miliary tubercle and the later weeks of typhoid, the leucocytes are diminished. Further details will be given under the special diseases.

#### LEUCOPENIA.

Definition.—A diminution in the number of white cells in the peripheral circulation as compared with the number normal for the given individual.

- 1. The effects of starvation and malnutrition in producing leucopenia have already been described. Such leucopenia is usually associated with lymphocytosis (see below). Cancer of the gullet is an example of this class.
- 2. Short hot baths or prolonged cold baths produce temporarily the same result (Winternitz, *loc. cit.*).
- 3. Most of the infective diseases in which there is no leucocytosis are sometimes characterized by leucopenia, e.g., grippe, measles, miliary tuberculosis, and other forms of pure tuberculous infection, malaria, and especially typhoid, in the later weeks of which it is almost invariable, and is accompanied by lymphocytosis.

When a case of leukæmia is complicated by an infective disease (pneumonia, septicæmia) the number of leucocytes may fall below the normal. In a case recently occurring at the Massachusetts

¹ Tuberculous meningitis often does show leucocytosis (vide infra, p. 282).

General Hospital in which a lymphatic leukæmia was terminated by septicæmia from glandular suppuration, the white cells fell gradually from 40,000 three weeks before death to 419 per cubic millimetre on the day of death. I have never heard of a lower count than this. The differential count was unchanged (lymphocytes = ninety-eight per cent).

- 4. In pernicious anæmia the count is usually very low and may fall below 1,000 cells per cubic millimetre. Other severe types of anæmia (rachitic, syphilitic, post-hemorrhagic) may produce the same result.
- 5. Splenic anæmia or the splenic form of Hodgkin's disease is often associated with marked leucopenia.

#### LYMPHOCYTOSIS.

Lymphocytosis is an absolute and relative increase in the circulating lymphocytes. The increase is relative to the number of lymphocytes normal for the individual. When lymphocytosis and an increase of the total leucocyte count are present we cannot distinguish the blood from that of lymphatic leukæmia, and the distinction must depend upon the course and symptoms of the case.

- 1. Such a condition (relative to the adult) occurs in healthy infants' blood and in many diseases of infancy, the blood seeming to have a tendency to return to the infantile type. This is especially true of cholera infantum, rickets, and any intestinal trouble. Anything that retards the infant's normal gain in weight or general development retards its blood development as well. Thus a child of three, convalescent from a summer diarrhæa, may have fifty to sixty per cent of lymphocytes, which would be normal for an infant of a few weeks, but for three years old is very high.
- 2. Pertussis, as Meunier has recently shown, is accompanied by a very marked lymphocytosis, the lymphocytes being quadrupled while the polynuclear cells are doubled. The increase is absolute as well as relative (see below, page 218).

Variola also shows lymphocytosis according to Weil.

3. Hereditary syphilis is perhaps the best known cause of relative lymphocytosis in children. Scurvy may produce the same result. Dividing the anæmias of children into two groups, those that do and those that do not produce leucocytosis, it appears that the

great majority of those whose total leucocyte count is normal show a relative lymphocytosis. This is the case irrespective of whether there is enlargement of the spleen or not.

Sometimes the smaller, sometimes the larger lymphocytes are in the majority. Often no division between the two kinds is possible.

- 4. In adults some forms of debility may be associated with an increased percentage of lymphocytes, due in fact to the absolute diminution of the neutrophiles. This should be distinguished from true lymphocytosis. The same false appearance of lymphocytosis may be seen in hæmophilia, goitre, cervical adenitis, and other conditions involving a diminution of the polynuclear neutrophiles, in chlorosis, pernicious anæmia, Graves' disease, and the anæmia secondary to syphilis, in the later weeks of typhoid fever and in lactation.
- 5. During the administration of thyroid extract, tuberculin, or pilocarpine.
- 6. The larger forms of lymphocytes are increased in some splenic tumors (chronic "ague cake"), and especially in the post-febrile stage of measles; also in many of the same diseases in which the small lymphocytes are increased.
- 7. The most marked absolute lymphocytoses known to me (excluding leukæmia) occurred in two cases of pertussis-pneumonia in infancy. One case occurred at the Massachusetts General Hospital in 1894—in a child of six, who passed through an attack of bronchopneumonia with uneventful recovery, the only peculiarity of the case being the marked increase of white cells running up to 94,600, sixty-nine per cent of which were lymphocytes. During convalescence the blood became normal and the child left the hospital entirely well. In 1900 we had a similar case in a baby of fifteen months, well until seized with paroxysms of coughing four days before entrance. The spleen and glands were normal. There were no hemorrhages and no anæmia. The blood showed

	White cells.	Per cent polynuclear.	Per cent lymphocytes.	Per cent. eosinophiles.	Remarks.
First day . Third day . Fifth day . Sixth day .	104,850	35	64.5	0.5	Red cells normal. No nucleated forms.

Since reading Meunier's account of the enormous lymphocytosis of *whooping-cough* I have believed these two cases to have been atypical whooping-cough. These cases will be referred to later in the account of the blood of pneumonia.

## Diagnostic Value of Lymphocytosis.

- 1. I have already suggested that the degree of health in persons not organically diseased might perhaps prove to vary directly with the percentage of polymorphonuclear cells in the blood.
- 2. In children the same percentage is to a certain extent a measure of the child's degree of development—causes of leucocytosis being excluded, and the percentage normal for a child of the patient's age being taken as the standard.
- 3. The diagnosis of obscure syphilitic disease may be supported by the coincidence of lymphocytosis with eosinophilia.
- 4. Absolute lymphocytosis in the presence of glandular tumors is our mainstay in the diagnosis of lymphatic leukæmia, but whooping-cough must always be remembered as a source of error.

### Eosinophilia.

Definition.—An increase in the number of eosinophiles in the circulating blood.

# Physiological Eosinophilia.

- 1. In the majority of *infants* the eosinophiles are much more numerous than in adults. Taylor has noted as many as 2,200 per cubic millimetre in healthy babies.
- 2. A temporary increase occurs during menstruation (eight per cent, Zappert).

Among the causes of pathological eosinophilia are:

- 1. Bronchial Asthma and Fibrinous Bronchitis.—During paroxysms the eosinophiles are plentiful in the sputum and in the mucous membrane of the upper air passages as well as in the blood. In the case quoted from Billings (see below, p. 340) there were 53 per cent of eosinophiles in a leucocyte count of 8,300. Gabrit-schewsky reports 22.4 per cent in asthma.
- 2. Acute and Chronic Skin Diseases.—The most marked cases are those reported by Lazarus (60 per cent of eosinophiles in urticaria (widely distributed), Zappert (33 per cent, or 4,800 eosinophiles per cubic millimetre in pemphigus), and by Canon (17 per

cent in prurigo and psoriasis). In dermatitis herpetiformis high eosinophile counts are reported by Leredde and Perrin, by Brown, and by myself (see below, p. 442).

3. Helminthiasis.—Trichinosis and ankylostomiasis are the members of this group which have been most thoroughly studied, and in both of them eosinophilia is marked and constant (see pages 434 and 428).

Bücklers working under Leichtenstern has established the interesting fact that "all varieties of helminthides from the harmless oxyurides to the pernicious ankylostoma may bring about an increase of eosinophiles in the blood, often to an enormous extent." Bücklers reports 16 per cent of eosinophiles in oxyurides, and 19 per cent in ascarides, and Leichtenstern has quite recently found 72 per cent of eosinophiles in ankylostomiasis and 34 per cent in a case of tænia mediocanellata (Ehrlich and Lazarus, p. 429).

4. Post-Febrile.—At the height of most acute infectious fevers (except scarlet fever and sometimes rheumatic fever) the eosinophiles are greatly diminished or absent. In the post-febrile period, however, abnormally high percentages of eosinophiles are often found.

Türck found 5.67 per cent (430 absolute) after pneumonia; 13.8 and 9.37 per cent (970 absolute) after rheumatism. Zappert found 20.34 (1,486 absolute) after malaria; 26.9 per cent (3,220 absolute) after tuberculin reaction fever. Grawitz found 90 per cent (!) (41,000 absolute) after tuberculin reaction fever (see page 272).

5. Malignant Tumors.—Various authors (Weiss, Palma, Rieder) have observed a slight eosinophilia in connection with the cachexia of malignant disease. It is, however, of moderate degree and seldom exceeds 7–10 per cent.

In Reinbach's study of 40 cases there were 4 with eosinophilia as follows: Sarcoma of the forearm, eosinophiles 7.8 per cent; sarcoma of the femur, eosinophiles 8.4 per cent; malignant tumor of the abdomen, eosinophiles 11.6 per cent; lympho-sarcoma of neck with ulcerative endocarditis and metastases in the bone marrow, eosinophiles, 48 per cent (60,000 absolute), see p. 368.

Among my cases there is one of generalized sarcoma with eosinophiles 12.4 (2,108 absolute). Zappert quotes a case of lymphosarcoma with 17.7 per cent (2,077 absolute) and 2 cases of cancer (uterus and stomach) with 11 per cent (860 absolute) and 8.5 per cent (535 absolute).

- 6. Compensatory Eosinophilia.—Ehrlich's researches appear to show that when the function of the spleen is abolished, either by splenectomy or by disease, a late compensatory eosinophilia occurs.
- 7. Medicinal Eosinophilia.—After the administration of camphor, v. Noorden observed an eosinophilia of 9 per cent in 2 chlorotic girls. Phosphorus poisoning is also said to cause eosinophilia, and Taylor refers to nuclein and pilocarpine as possessed of similar properties.
  - 8. Myelogenous Leukæmia (see below, p. 168).
- 9. Eosinophilia in Hæmatoma, Hemorrhagic Exudations, and Purpura.—Klein (Centralbl. f. inn. Med., January 28th, 1899) reports two cases of hemorrhagic pleural exudation with a very large number of eosinophiles (74 to 76 per cent) in the exudate and a marked increase of circulating eosinophiles:

Case.	Date.	Red cells.	White cells.	Per cent hæmo- globin.	Per cent poly- nuclears.	Per cent eosin- ophiles.	Per cent lympho- cytes.
1	March 29 April 4 April 11 (1893)	3,800,000	11.800 6,200 8,150	45	71.7 56.5 44.	12.5 37.5 40.	15.8 6. 16.
2			9,189		69.1 65.1	6.5 16.1	24.3 18.7

Perhaps of a similar type is the eosinophilia exemplified in the following report from a case of simple purpura in a girl of eight. White cells, 18,000; eosinophiles, 17.5 per cent; polynuclears, 44 per cent; lymphocytes, 39 per cent.

## DIMINUTION IN EOSINOPHILES.

- 1. During digestion and severe muscular exertion.
- 2. After castration (Neusser).
- 3. In febrile stages of pneumonia, grippe, typhoid, diphtheria, sepsis, and most infectious diseases accompanied by leucocytosis. That this is not due simply to the presence of fever is shown by the fact that in malaria and scarlet fever, despite high fever, eosinophiles may be increased.
  - 4. In the moribund state eosinophiles are diminished or absent.
- 5. Malignant disease, hemorrhage, and most of other causes of leucocytosis also diminish the eosinophiles.

DIAGNOSTIC AND PROGNOSTIC VALUE OF EOSINOPHILIA.

In trichiniasis eosinophilia is of great diagnostic value.

Neusser has suggested the following points: 1

- 1. In the diagnosis between puerperal mania and puerperal sepsis, eosinophilia points to the former.
- 2. Between a tumor connected with the genital system and one not so connected, eosinophilia points to the former.
- 3. In determining whether a given case of hysteria, neurosis, or psychosis is likely to be benefited by castration, the presence of eosinophilia favors the operation.
- 4. In malignant disease an eosinophilia points to a metastasis in the osseous system (tumors of the spleen are not included in this rule).
- 5. In cases of doubtful syphilis eosinophilia combined with lymphocytosis (see above) speaks in favor of syphilis.
- 6. The diagnosis of any obscure form of "uric-acid diathesis" is helped by finding an increase of eosinophiles.
- 7. In distinguishing malignant liver disease from other liver disease eosinophilia points to the latter.
  - 1. In the prognosis of chlorosis, eosinophilia is favorable.
- 2. In the prognosis of scarlet fever and scarlatinal nephritis the greater the eosinophilia the better the prognosis.
- 3. After hemorrhage increased eosinophiles show active regeneration of blood and good prognosis.
- 4. In pernicious anæmia eosinophilia is favorable for the same reason.

#### MYELOCYTES.

The occurrence of the myelocyte of Ehrlich in the circulating blood is almost always to be looked upon as pathological, that is, as the intrusion of a variety of leucocyte naturally a stranger to the circulating blood and a permanent inhabitant of the marrow. Among hundreds of specimens from healthy persons I have seen but one typical myelocyte.

- 1. The largest number of circulating myelocytes occurs in myelogenous leukæmia (see page 161).
- 2. In all conditions associated with stimulation of the bone marrow—that is, in all diseases accompanied by well-marked leucocy-

<sup>&</sup>lt;sup>1</sup> For none of which I can vouch.

tosis or by severe anæmia of any type, myelocytes in small numbers may frequently be found. Thus I have found them in most cases of pernicious anæmia and of malignant disease with leucocytosis. Türck finds them in most acute infections, even in typhoid with subnormal leucocyte count. Engel has noted their frequent presence in diphtheria, while Neusser' has noted them in various toxic conditions such as puerperal mania, osteomalacia, uræmia, carbonicacid poisoning, Basedow's disease, diabetic coma. Others have recorded their occurrence in rickets, syphilis, phthisis, general paralysis, etc.

The common elements in these various diseases are anæmia and leucocytosis. Accordingly it seems to me reasonable to class them as signifying a marrow stimulation, and as much akin to Türck's "stimulation forms" (see above, pages 110 and 111).

The most curious example of their occurrence known to me is the following:

Mrs. W—— had been starving herself more or less for six months from motives of economy. Two weeks before I first saw her she began to suffer with cystitis. From both these troubles she made a rapid recovery, which has persisted now eighteen months. There was at the first count a leucocytosis of 15,100; partly due to cyanosis, as she had just been having a chill. The red cells were 7,300,000. Hæmoglobin, eighty-seven per cent. Differential counts were as follows:

Date. Number of cells counted.	May 2d 800. Per cent.	May 6th 1,000. Per cent.	400.	May 8th 400. Per cent.	May 13th 1,000. Per cent.
"Polynuclear neutrophiles" Lymphocytes Large mononuclear Myelocytes Eosinophiles.	8.6 8.2 .5	82.2 12.5 1.5 3.5 .3	83.6 9.4 2.0 4.0 1.0	80.2 11.3 6.0 2.5 .0	68.5 25.2 5.2 .6 .5

In a general way their presence seems to have about the same significance as that of normoblasts, but they occur much more frequently. As a rule I think they indicate an acceleration of the marrow functions by which red corpuscles and granular leucocytes are furnished to the blood. Such an acceleration may be supposed to take place in leucocytosis, leukæmia, and severe anæmia, which are the chief conditions in which myelocytes appear in the blood.

<sup>&</sup>lt;sup>1</sup>Cited in Klein: Volkmann's "Samml. klin. Vorträge," December, 1893.

## CHAPTER IX.

GENERAL PATHOLOGY OF THE BLOOD AS REGARDS HÆMO-GLOBIN, FIBRIN, LIPÆMIA, MELANÆMIA, AND HEMORRHAGE.

#### Hæmoglobin.

As stated above, the hæmoglobin may increase and diminish in lines parallel to those of the red cells. In that case we suppose the amount of hæmoglobin per corpuscle to be normal and the color index or valeur globulaire is said to = 1. When the hæmoglobin is diminished more than the count of corpuscles, we say that the color index is less than 1. For example, if a man has 5,000,000 red cells per cubic millimetre and only 50 per cent of hæmoglobin, we estimate the color index by simply reducing the count of cells to a stated percentage (5,000,000 cells = 100 per cent of cells) and dividing this percentage into the hæmoglobin percentage—i.e.,  $\frac{5.0}{10.0}$  = 0.5 = the color index. Therefore 4,000,000 red cells (= 80 per cent) with 60 per cent of hæmoglobin give a color index of  $\frac{6.0}{8.0}$  = 0.75.

The color index rarely goes above 1, except in pernicious anæmia (see below). Here it may be as high as 1.7. As a rule when the red cells are above the normal the hæmoglobin rises equally, sometimes it lags behind a little, but rarely if ever does it rise higher than the cells.

In most anæmias, as has been pointed out, the hæmoglobin suffers markedly before any considerable loss of red cells takes place. In other words, the corpuscles seem to get thin before they die, and except in malaria, hemorrhage, and a few other cases they are not destroyed while in the full vigor of health.

The loss of hæmoglobin is loss of albumin, the chief constituent of the cells, and hence is usually loss of weight.

In general the changes in the hæmoglobin are best studied in con-

<sup>1</sup>This is of course not literal. There is no reason to suppose that goodsized corpuscles get smaller. It is more likely that a smaller generation is sent out by the blood-making organs. FIBRIN. 121

nection with changes in the count of red cells, and so far as they have not already been mentioned will come in under the various special diseases.

#### FIBRIN.

The fibrin network to be seen in normal blood during coagulation (see page 54) is increased in a considerable number of conditions. Hayem has studied these minutely, and described several varieties of arrangement of fibrin fibres as characteristic of special diseases, that is, he studied fibrin qualitatively as well as quantitatively, and also as regards the rapidity of its formation.

The rate of fibrin formation is often not the same as the rate of coagulation. It is not parallel to the number of leucocytes or blood plates, at least not in all cases (malignant diseases, scurvy).

In a general way we expect increased fibrin in infectious and inflammatory diseases, but there are notable exceptions to this. The greater the exudation and the freer it is (in a cavity or on the surface) the thicker the fibrin network, while so-called interstitial inflammations or such conditions as parenchymatous nephritis show little increase in fibrin. The seat of the lesions has no considerable influence, except as it modifies the nature of the lesion. An abscess in one place has the same effect as an abscess elsewhere, provided it is equally free or equally confined, and of the same contents.

Tuberculosis does not increase fibrin if uncomplicated. Leucocytosis and fibrin behave alike in many respects, especially in relation to the vigor of resistance which the individual opposes to a given infection. When the individual is so weakened that he does not react well against the infection, the leucocytes and fibrin are but slightly increased, whereas in a vigorous individual the same infection would have markedly increased both fibrin and leucocytes. But neoplasms raise the count of leucocytes without changing the amount of fibrin.

In a general way fibrin increases and decreases as fever does, but often persists after fever is gone.

The most marked fibrin networks are seen in pneumonia, acute articular rheumatism, suppurative diseases, and in scurvy. In erysipelas it follows the leucocytes (increased in severe, not in mild cases). In the early days of grippe it is increased.

The fever of hysteria or chlorosis shows no increase of fibrin, and post-hemorrhagic anæmia with or without fever shows none.

Fibrin is diminished in pernicious anæmia, not increased in leukæmia, typhoid, malaria, malignant disease, non-suppurative diseases of liver, nephritis (except interstitial nephritis, in which it may be increased), heart disease, purpura, hæmoglobinuria (sometimes decreased).

The most valuable point about the fibrin appears to be the absence of any increase in malignant disease, whereby a diagnosis between the affection and a suppuration may be helped. Otherwise the information given by it is chiefly confirmatory of impressions given by other features in blood examination.

#### LIPÆMIA.

The blood invariably contains small quantities of fat, especially during digestion (v. Jaksch 1).

In the blood of persons suffering from a variety of diseases such as phthisis, diabetes mellitus, obesity, alcoholism, nephritis, and in some dyspnœic conditions, suppressed menses, pregnancy, icterus, typhus, malaria, mental disease, diseases of the heart and pancreas, as well as in health, fat is occasionally to be seen in considerable quantities. Grawitz² finds that if the blood is collected in a fine capillary tube and this is kept in a horizontal position for some time, fat rises to the surface like cream, and can be seen with an oil-immersion lens in the form of fine drops. Gumprecht³ demonstrated it with osmic acid, which stains the fat drops black, and proved them to be fat by dissolving them in ether, xylol, etc.

Lipæmia has no special significance so far as is known, and is not characteristic of the diseases above mentioned. Its cause is unknown.

[In almost any preparation of the fresh blood fat drops are to be seen unless the patient's skin is washed with alcohol before puncturing. Even with these precautions a few drops may often be seen in healthy people's blood.]

#### MELAN.EMIA.

In malaria the occurrence of a black pigment in the leucocytes which have taken plasmodia into themselves, is generally to be seen during and shortly after a paroxysm. Pigment free in the blood is to be seen only at the moment of segmentation among the new

 $^1$  "Klin. Diagnostik." p. 75 (English translation).  $^2$  Loc. cit., p. 160.  $^3$  Deut. med. Woch., 1894, No. 39.

generation of parasites. The same condition has been observed in relapsing fever and in persons suffering from melanotic malignant tumors, the pigment being always in the white corpuscles. Presumably it must at some time be free in the plasma, but it is rarely if ever seen outside the cells.

In Addison's disease Tschirkoff  $^{\mbox{\tiny 1}}$  observed pigment in the leucocytes.

#### HEMORRHAGE.

Women can stand a greater hemorrhage than men. Children, on the other hand, succumb to comparatively slight hemorrhages (cf. Blood in Infancy, page 445). Individual differences make a great difference in the ability to survive hemorrhage, and no exact amount of blood can be stated as the maximum that any one can lose and yet survive.

Changes in the Blood Resulting from Hemorrhage.

The red cells and hæmoglobin of course suffer proportionally at first; later the hæmoglobin in the newly formed cells is always deficient (see below).

The striking point in the blood after hemorrhage is the evidence it gives us that even before the hemorrhage has ceased the other tissues begin to contribute fluid to make up the *volume* upon which life depends. The serum is markedly diluted by this fluid, but still serves to give the heart something to contract on and so prevents blood pressure from falling as fast as it otherwise would do. Were it not for such contributions from neighboring tissues the organism could sustain but slight hemorrhage without succumbing at once. We have then after hemorrhage a diluted or hydræmic blood, even though we do not assist the efforts of nature by contributing fluid by intravenous or rectal injection. Behier reports a case due to trauma in which the count was only 688,000 per cubic millimetre.

Coagulation increases in rapidity the more blood is lost, so that after severe hemorrhage it takes place almost instantly.

## BLOOD REGENERATION.

The regeneration of the blood after hemorrhage may be taken as typical of the same process in anæmia from other causes.

<sup>1</sup>Zeit. f. klin. Med., vol. xix., 1891.

The length of time needed for full restoration to normal depends not merely on the (a) amount of blood lost, but also on the (b) age and nutrition of the patient as well as upon (c) the methods of treatment carried out and the existence of (d) other disease (typhoid, malignant disease, phthisis, etc.).

Allowing for these other conditions we may say that, other things being favorable, the loss of

I. Less than 1 per cent of the blood mass is made up in 2 to 5 days. II. From 1 to 3 " " " " " 5 " 14 " III. " 3 " 4 " " " " " 14 " 30 "

The last amount means a very severe hemorrhage. Few surgical operations involve the loss of over three per cent, and after such accordingly we expect the blood to be normal again in two weeks, provided the individual is otherwise sound (see Malignant Disease, page 373).

Young, well-nourished persons are of course quicker in making up losses than the old and weak.

## Blood Condition During Regeneration.

- 1. Red Cells.—(A) As previously mentioned, the hæmoglobin becomes relatively low as soon as the regenerative process is well established, and as recovery progresses the red cells are almost always normal in numbers for some time before the stature, weight, and color of the individual cells is what it should be. A color index of 0.50–0.60 is not unusual—in short, what some call a "chlorotic" condition of the blood.
- (B) Qualitative changes are those already described on page 83, namely: (a) Deformities in size and shape with an average diminution in size; (b) polychromatophilic cells; and (c) nucleated corpuscles. These latter are almost exclusively of the normoblast type, but an occasional megaloblast has been observed.

Blood Crisis.—Von Noorden was the first to notice that in some cases nucleated corpuscles are to be found in the circulation in great numbers for a few hours only, the blood examination both before and after showing few or none at all. The name of "blood crisis" has been given to these sudden outpourings of nucleated red cells; they are to be observed during recovery from various forms of anæmia.

2. White Cells.—Immediately after a loss of blood we can usually find a decided *leucocytosis* despite the dilution of the blood (see above, Post-hemorrhagic Leucocytosis).

This leucocytosis is in no way different from those occurring from other causes. The percentage of polymorphonuclear cells is usually increased, and the eosinophiles often disappear. As pointed out by Stengel we may have a lymphocytosis after hemorrhage, either from the start or following a polynuclear leucocytosis. In his case the percentages were: Polynuclears, 43.5; lymphocytes, 43.5; transitionals, 10; eosinophiles, 2.8. A case of anæmia from bleeding piles, in which the red cells were 2,723,000 and the hæmoglobin 35 per cent, showed in a total leucocyte count of 4,200, 69 per cent of small lymphocytes and only 28 per cent of polymorphonuclear cells. Leucocytosis if present is rarely very high, seldom reaching over 30,000. It is not invariably present, or if present sometimes is of very short duration. Thus in a patient whose red cells were reduced to 3,200,000 by a profuse uterine hemorrhage the white cells counted next day were only 8,000; while in the next bed of the hospital was a woman crushed in a railroad accident whose red cells were 1,280,000, and the white cells 28,000, the usual state of things.

The leucocytes may be increased even by a *cerebral hemor-rhage* which is not large enough considerably to affect the red cells in most cases. Ten apoplectic cases (with autopsy) observed at the Massachusetts Generai Hospital showed such counts as the following:

- 1. Red cells 5,512,000, white cells 25,000, Hb. 85 per cent.
- 2. Red cells 5,560,000, white cells 15,600, Hb. 90 per cent.

Whether the leucocytes are here affected by any influence other than that of hemorrhage I do not know.

The effect of transfusion (intravenous saline solution) is apparently at first to increase the leucocytosis.

D——, a patient with traumatic rupture of the urethra, had had severe hemorrhage for forty-eight hours before it was checked at 1 P.M., November 1st, 1895. At 4 P.M., his pulse being 165, the count showed red cells, 3,304,000; white cells, 10,400. He was at once given a pint of sterilized normal salt solution by intravenous injection under the strictest asepsis. Ten minutes after the transfusion the leucocytes numbered 32,400. One hour later, they were 24,700, and the red cells 3,632,000. Four hours later,

leucocytes, 31,900; red cells, 3,046,000. The later counts were as follows:

		Red Cells.	White Cells.
Novembe	r 2d: good pulse	3,608,000	34,600
**	2d (5 p.m.): good pulse	2,944,000	30,200
**	3d (4 p.m.): good pulse	2,928,000	15,800
**	13th	3,360,000	16,600

A good recovery was made.

# IMPORTANCE FOR SURGERY OF BLOOD COUNTING AFTER HEMORRHAGE.

Mikulicz, who as a surgeon should speak with authority and who always takes account of the condition of the blood in his cases, lays down (following Laker) the following rule: Never operate on any case when the hæmoglobin is below thirty per cent. The question of operating at once or waiting for recovery from "shock," is a very common one in the accident rooms of any hospital and is generally settled on general impressions of the patient's vigor. We know, say, that he has lost blood, but we have no way of ascertaining how much. If his "shock" is due to hemorrhage he may need transfusion; if it is due to cerebral concussion or compression, the transfusion will do more harm than good. The blood count can settle these questions, and could reveal much which is now obscure, if it were more frequently employed in surgical cases and a standard like that of Mikulicz worked out.

In cases of suspected ruptured tube in extra-uterine pregnancy, the question of whether the patient is suffering from internal concealed hemorrhage can be settled in many cases by the blood count, which will show a decided loss of red cells if the hemorrhage is large, and thereby distinguish the condition from peritonitis, obstruction, or strangulated hernia, none of which affects the red cells. Any other concealed hemorrhage, as for instance from ruptured kidney or spleen or liver, may be indicated by the blood count when by other physical signs the diagnosis might be very difficult.

## Summary.

The blood count is of importance after cases of supposed hemorrhage.

- 1. To ascertain whether such has taken place.
- 2. Its extent.

- 3. Whether operation is to be immediate or not.
- 4. Whether transfusion is indicated.
- 5. How soon the patient has got back enough blood to make operation worth while.

### CHRONIC HEMORRHAGE.

Piles, uterine disease, hæmophilia, purpura, and other causes may produce a long-standing drain on the blood.

Some patients apparently can lose a little blood almost daily for years without acquiring any severe anæmia, and if the individual is otherwise sound and does not suffer from an underlying disease like phthisis, cancer, or nephritis, he can probably go on for a long time without showing any bad effects from the repeated small hemorrhages. How much he can stand we have no way of judging, for we cannot measure the amount of blood lost. When, however, such small repeated losses do produce an anæmia, regeneration is apt to be much slower than after a single large hemorrhage. The longer the drain has been going on the poorer the chance for recovery, and the slower the latter will be if it does take place.

Gain in body weight does not always mean gain in corpuscle substance as well (see Malignant Disease, page 373).



# BOOK II.

SPECIAL PATHOLOGY OF THE BLOOD.



# PART I.

## CHAPTER I.

## THE PRIMARY ANÆMIAS.

#### 1. THE BLOOD IN PERNICIOUS ANÆMIA.

1. Volume and Oxygen Capacity.—J. Lorrain Smith, studying the blood of seven cases by the carbonic-oxide method, concludes that "absolute loss of oxygen capacity (= hæmoglobin), which in chlorosis practically does not occur, is here of primary importance. Whereas, in chlorosis, the oxygen capacity is 95 per cent of the normal, here it averages 48 per cent, and in one case was but 28 per cent."

The volume of blood is sometimes markedly increased, sometimes normal, sometimes diminished. Patients with a large volume of blood seem to feel worse than those with normal volume, even when the hæmoglobin percentage and count of corpuscles are approximately the same. In the remissions of the disease the volume may be rapidly reduced. So, for example, 4,305 e.e. with 1,100,000 red cells per cubic millimetre and later (in remission) 2,775 c.c. with 3,104,000 red cells per cubic millimetre.

- 2. Gross Appearances.
- (a) The drop as it emerges from the puncture is often excessively pale and watery, but not more so than may occasionally be seen in secondary anæmia or chlorosis. Sometimes it is not nearly so pale as in other cases with equally low counts, a fact which may be due to the increased color index sometimes present (see below).

In several early cases I have seen the blood as red as normal.

Another appearance, which I have frequently observed in this and other anemias, is an uneven, streaked color in the drop, as if the cells were unequally divided in the plasma.

(b) As striking as the color of the drop is its great fluidity; the rapidity with which it slips off the ear or finger often makes it diffi-

cult to suck it up in time. It is usually very slow in coagulating. When drawn the blood does not separate into serum and clot, even after the lapse of seventy-two hours (Lenoble).

(e) The fresh specimen in most cases shows no rouleaux formation, and a marked diminution in blood plates and fibrin. Hayem says: "This double lesion, rarity of blood plates and loss of retractility on the part of the clot, is, according to my latest observations (1900), the most characteristic sign of this form of primary anæmia." I have no experience on this point.

There are usually great variations in the size and shape of the corpuscles with a tendency to an oval shape and an increase in the average diameter. Not infrequently the deformed corpuscle shows active pseudo-amœboid motions of its projecting points or of the cell as a whole. The great lack both of red and white cells is noticeable even in the fresh specimen.

## Red Cells and Hæmoglobin.

(a) Quantitative changes (see Table I.). The average count of red cells in the one hundred and ten cases of my table is about 1,200,000, which may be taken as the average count in patients seen at the stage of the disease at which they feel sick enough to seek medical advice. We very rarely get an opportunity to examine the blood in the early stages of the disease, so that we have to judge of them chiefly from the evidence given during the remission so commonly observed. In the relapse following such a remission the blood count may fall from 5,000,000 to 1,000,000 in a period of from six weeks to six months. In the later stages of the disease 500,000 red cells per cubic millimetre is not rare, and if the diminution has been gradual, the patient may be up and about and able to do light work with a count no greater than this. I had an opportunity to observe such a case in the wards of Dr. F. C. Shattuck at the Massachusetts General Hospital five years ago, in which for several weeks the blood count remained at or near 500,000, yet the patient was outdoors daily, read the papers, and seemed perfeetly comfortable. Evidently it is not the anæmia itself which kills the patient.

The lowest count on record is that reported by Quincke—143,000 per cubic millimetre. This case later improved so much that the

 $<sup>^1\</sup>mathrm{Cf.}$  Schaumann: Out of his 38 cases, 1 was over 2,000,000; 26 were between 1,000,000 and 2,000,000: 11 below 1,000,000; average 1,290,000.

corpuscles rose to 1,234,000 within seventy-four days of the count of 143,000. She lived several months "fat and well nourished."

# $\begin{array}{c} \textbf{Table I.} \\ \textbf{Pernicious Anæmia}^{\scriptscriptstyle 1} \ (110 \ cases). \end{array}$

T	he red cells	ranged:							
	From 500,0	000 to 1,000	,000 i	a				· <b></b>	27
									45
9	" 1,500	0,000 to 2,0	00,000	in					34
	m		3 0					-	100
									106
	From 2,000	0,000 to 2,5	00,000	in	• • • •				4
									110
Ъ.	Leucocytes	numbered	:						
							, .		9
	1,000 to 3,	000							23
	3,000 to 5	,000							40
	5,000 to 7,	.000							24
									12
	10,000 to 1	3,000			• • • • •			• • • • • • • • • • • • •	2
								•	110
c	Hæmoglob	in:							
٠.			n						79
									31
			_						
									110
d.	Average d								
								• • • • • • • • • • • •	89
	Not in	creased in.	• • • • •					• • • • • • • • • • • • • • • • • • • •	21
									110
е.	Megaloblas	sts at time	of firs	t exan	ninat	ion:			
•									87
									20
	Only o	ne examin	ation,	no me	egalo	blasts	8		. 3
									110
									110
f.	0 1		-		t and	-		in	34
	44	44	30	46	44	40	46		34
	"	44	40	66	"	60	46		33
	44	46	60	66	"	80	44		6
		**	80		**	90		* * * * *	3
									110
	<sup>1</sup> For co	omplete rec	cords	of the	se ca	ses se	e App	endix B.	

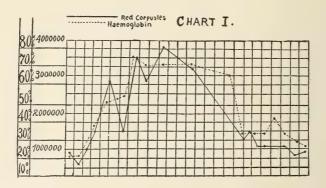
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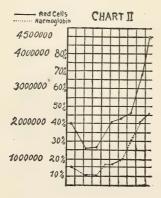
Under 4	per cent		90
			110
1 .	70	Highart nonconta	

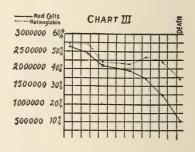
# h. Myelocytes. Present in 66 cases. Highest percentages:

10	per cent	in.									 					 													 							2	ì
9	66																																			1	
8	66	11																																		2	
7	66	44																																		9	8
			٠		•	•	•	•	•	•		•	•	•	• •	•	٠	•	٠	•	•	•	•	•	•	•	• •	• •	•	•	•	•	•	•	_	10	
																																				1	

The great but temporary improvements above alluded to, followed by relapse, occur either with or without treatment. In the course of a few months the count of red cells may rise to normal, the nucleated corpuscles (see below) disappear, and the patient is







apparently restored to health and goes to work with a laugh at the doctor. I have followed one case through five such relapses in a period of three years before the fatal issue came. Frequently the patient feels so well during one of these remissions that he goes to work and is lost sight of, and, under such conditions, the incautious are apt to report "cure."

The accompanying charts' show the three types usually met with; No. II. being, of course, only a fragment of a case similar to No. I., while the steady progression of No. III. may have been preceded by a rise from a former downfall, though no such history was obtained.

Looking over a considerable number of cases, one can hardly help being struck with the tendency of the count to remain near the figure 1,000,000. The red cells rarely remain stationary at, say, 2,000,000, and often death may occur without the red cells sinking below 1,000,000. It seems as if some self-applying mechanism tended to arrest the destruction of corpuscles at or near this point.

In counting the red cells some difficulty and error may result from the very small size of some of the cells. It is especially important that the diluting solution should be clean and freshly made, else without the aid of a stain it may be hard to distinguish the dwarf cells or microcytes from bits of extraneous substance.

## QUANTITATIVE CHANGES.

White Corpuscles (see Table I.).—The rule is a very considerable diminution in the number of leucocytes. Thus of 110 cases which I have examined 71 were under 5,000, the average of all being 3,800.

[I have excluded from this series counts made immediately after hemorrhages and counts in infants. The latter are very apt to show a leucocytosis in connection with *any* form of anæmia.]

As the disease progresses the leucocytes fall even more rapidly than the red cells, and counts as low as 500 white cells per cubic millimetre are not uncommon.

Leucocytosis when present in the blood of adult cases is always due to some complication like hemorrhage or suppuration.

As mentioned above, the blood plates and fibrin are much diminished.

<sup>&</sup>lt;sup>1</sup>The number of perpendicular lines represents the number of weeks.

No.	White cells.	No.	White cells.	No.	White cells.
1	400	21	2,900	41	4,828
2	500	22	3,000	42	4,900
3	800	23	3,000	43	5,000
4	1,000	24	3,200	44	5, 200
5	1,000	25	3,200	45	5, 300
6	1,000	26	3,300	46	5,500
7	1.500	27	3,400	47	5,600
8	1,600	28	3,500	48	6,000
9	1.800	29	3,600	49	6,000
10	2,000	30	3,700	50	6,000
11	2,000	31	3,704	51	6,400
12	2,000	32	4,000	52	6,500
13	2,000	33	4,000	53	7,000
14	2,000	34	4,000	54	7,200
15	$\frac{2,000}{2,300}$	35	4,000	55	7,500
16	$\frac{2,500}{2,600}$	36	4,200		7,600
17	$\frac{2,000}{2,800}$	37	4, 300	56	9,000
				57	. ,
18	2,800	38	4,400	58	9,600
19	2,800	39	4,500	$\begin{bmatrix} 59 & \dots \\ 60 & \end{bmatrix}$	10,000
20	2,800	40	4,720	60	10,100
		1		Average	= 3,800 +

TABLE II.—WHITE CELLS.—FIRST EXAMINATION IN SIXTY CASES.

In four cases in which Dr. Lindström, of Boston, was kind enough to give massage, we were unable to see the slightest gain either in corpuscles or hæmoglobin, such as can be produced temporarily in most healthy persons. The observations of J. Mitchell on this point we were unable to confirm.

# Hamoglobin.

The great majority of cases of pernicious anæmia have a relatively high percentage of hæmoglobin (e.g., 1,000,000 red cells and 35 per cent of hæmoglobin, or a color index of 1.75). Ehrlich has several times found it over 50 per cent even in the severest cases, and once as high as 65 per cent.

This high color index is not, however, peculiar to this disease. The same condition has been noted in acute leukæmia, in "splenic anæmia" (McCrae), and in leprosy.

Of the 110 cases in the series on page 133, in which the hæmoglobin was tested, a color index of over 1 was apparently present in 79, or 71 per cent, and a color index of less than 1 in 31, or 29 per cent, of the cases. How many of these hæmoglobin estimations may have been wrong I cannot say.

From the frequency with which we find the corpuscles well stained and larger than normal in pernicious anæmia (see below), we

should expect that the hæmoglobin would be relatively high, and in a larger percentage of cases than the v. Fleischl instrument indicated.

An increased color index is probably a bad prognostic sign. In the remissions of the disease when the cells are increasing fast, the hæmoglobin lags behind and the color index is low. As the relapse follows, the color index in many cases progressively increases. Cases whose color index is low and in which the average diameter of the red cells is normal are apt to be gaining at that time, while those with high color index are apt to be losing at that time.

The average color index in the cases in which the hæmoglobin and red cells were both tested was 1.04, the average percentage of hæmoglobin being 26 and of corpuscles 24 (= 1,200,000).

## QUALITATIVE CHANGES.

## 1. Red Corpuscles.

We must distinguish here between

I. The active stages of the disease and

II. The remissions.

In the active stages we find:

(a) Increase in the average diameter of the cells is a very constant and striking feature of the stained specimens in this disease. In no other disease do so large cells or so many of them occur.

The average diameter may rise as high as 11 to  $13\,\mu$ , but as a rule the average is reduced by the presence of a few abnormally small forms. The percentage of oversized cells gives us a better idea of the facts. Thus Ehrlich in 8 cases of pernicious anæmia found the following percentages of oversized red cells: 71, 71, 66, 65, 60, 58, 57, 56.

Out of one hundred and ten cases in which I have looked for this point, eighty-nine showed the increase, as far as could be judged without measuring any large number of cells. This does not mean that every cell is larger than normal, but that those larger than normal outnumber those undersized; the "macrocytes" are more numerous than the "microcytes." Occasionally we see cells over  $20~\mu$  in diameter, some with nuclei, some without.

(b) Deformities in Shape.—The eye soon gets used to the shapes assumed by the necrobiotic corpuscles and learns to distinguish them from the distortions due to technique or to crenation. Most of them fall under one or another of the types shown in Plate IV. The very

large forms are generally oval, but seldom present any further deformities. Among the smaller cells the battledore and sausage-shaped forms are very common. In one case I found all the red cells of the latter shape, so that they looked at first sight like a lot of gigantic bacilli. That this appearance was not due to the technique¹ (as I had at first supposed) is probable from the fact that the rod-shaped cells did not point all in one direction as they would have done if pulled out of shape by the process of spreading (see Fig. 29). This appearance is only an exaggeration of what may be

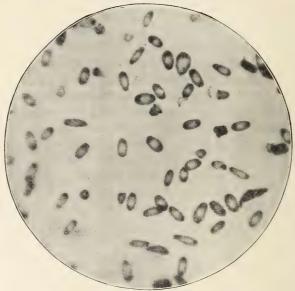


Fig. 29.—Elongated or Oval Corpuscles in Pernicious Anæmia.

seen in most severe anæmias, namely, a tendency toward an oval shape like that of amphibian corpuscles. This is usually true of those cells (in pernicious cases) which are not more violently deformed. The type of cell so common in secondary anæmia—well stained at the edges and pale in the middle (Litten's "pessary forms") are rarely seen.

Occasionally we see cases with no considerable deformities whatever in the red cells. In nine cases out of sixty in which this point was observed, little or no deformity was noted. I cannot make out

 $<sup>^1</sup>$  Some writers advise the use of less heat than usual in dealing with coverglass specimens of pernicious anæmia. I have not found this so, and heat as usual up to  $150^\circ$  C. and then stop.

that such cases have any better or worse prognosis than others. I have never seen cases whose red cells were all *undersized*, but a normal average diameter was present in somewhat under one-quarter of the cases in which I have looked out for this point.

(c) Staining Properties of the Red Cells.—The white spots or streaks described by Maragliano, Hayem, and others are very often seen in the red cells of pernicious anæmia despite good technique. Some corpuscles are so pale in the centre that we see only the narrow ring of stained protoplasm at the periphery, a mere shell. Others are swollen up so as to show no sign of central biconcavity, and stain deeply and evenly all over.

More common than in any other form of anæmia are the polychromatophilic red cells (see Plate IV.) which with the Ehrlich-Biondi mixture stain brownish, purple, or gray, either as a whole or in parts. In cover-slips stained with thionin the spotted appearance of the protoplasm described by Ehrlich and Grawitz is usually marked. In the nucleated red cells the protoplasm is very apt to show these changes. In some cases it is difficult to distinguish normoblasts from lymphocytes. In difficult cases we have sometimes to fall back upon the appearances of the periphery, which in most red corpuscles shows some thin place or crinkle characteristic of a flat cell, while the lymphocyte gives us the more solid-looking outline of the spherical cell.

All these microchemical changes can be better brought out with hæmatoxylon-eosin or eosin-methyl-blue stains, but all that is needed for clinical purposes can be made out with the ordinary Ehrlich-Biondi mixture.

# 2. Nucleated Red Corpuscles.

Nothing further needs to be said in description of these forms (see above, pages 89–93). We have no exact method of estimating the number of nucleated cells either in relation to the whole number of red cells or in a cubic millimetre. All we can do is to note the number seen in such an area of a cover-glass specimen as is covered while counting a given number of white cells, say 1,000. Knowing the ratio of red to white corpuscles, we can calculate from this number of nucleated red cells their approximate relation to the whole number of red cells.

Thus if the ratio of white to red be 1:1,000 (1,000,000 red and 1,000 white) and we have seen two nucleated red corpuscles while making a differential count of 1,000 white cells, the total number of red cells passed over must be approximately 1,000,000 and the

number of nucleated corpuscles about 2:1,000,000 red cells or two in a cubic millimetre. Of course when leucocytosis is present and the ratio is raised—say to 1:150 (10,000 white and 1,500,000 red)—finding two nucleated red cells while counting 1,000 white would mean that there were two nucleated cells in every 150,000 non-nucleated, or twenty in a cubic millimetre (or in 1,500,000 non-nucleated cells).

Such calculations are inaccurate because we are never sure that the red cells and white cells are distributed in the dried specimen exactly as they are in the blood. Part of the leucocytes may be accumulated at the edges of the cover-glass so that the ratio in the middle may be different from that in the circulating blood.

Nevertheless we can get some idea of how plentiful the nucleated corpuscles are, and as their significance in prognosis depends far more on their kind than on their number, greater accuracy as to the latter is not at present important. For instance, two megaloblasts per cubic millimetre mean a worse prognosis than twenty normoblasts, provided there are no other kinds present in either case. It is the ratio of megaloblasts to normoblasts and not the absolute number of each, that is of importance.

In all but three of the cases of pernicious anæmia in which I have examined the blood, the number of megaloblasts has exceeded the number of normoblasts, and as the cases grew worse the megaloblasts grew relatively more numerous (often absolutely as well). Further, in several hundred cases of severe secondary anæmia I have never yet seen the number of megaloblasts exceed the number of normoblasts.

The range of variation in the number of nucleated cells present has extended in my series from 6 per cubic millimetre to 7,100 per cubic millimetre (see Table III.). The calculation can be made by using the following formula:

Let n = the number of white cells counted (by differential count).

- " m = " nucleated red cells seen while counting these.
- " p = " white cells per cubic millimetre (Thoma-Zeiss).

 $p \times \frac{m}{n} = x = \text{number of nucleated red cells per cubic millimetre.}$ 

The search for nucleated corpuscles in pernicious anæmia is sometimes the most laborious undertaking in all blood examination, but it is also one of the most important. We may search two or three hours before finding one nucleated corpuscle, but on that corpuscle may hang the character of our prognosis. If it be a megalo-

blast and no other nucleated red corpuscles are seen, the prognosis is bad, and it is important that we should know it. This is particularly true when the case is seen during a remission, for under these conditions we might never suspect a case of pernicious anæmia but for the presence of megaloblasts. They are not always difficult to find; indeed, in one of my cases they were nearly as numerous as the white cells, but, as a rule, we do not get off with less than two hours' work.

The number of megaloblasts in the peripheral circulation often varies very markedly from day to day so that to-day it may be almost impossible to find any, while to-morrow they will be plentiful. Even in different preparations made at the same time the number of megaloblasts may vary greatly. The importance of frequent examinations is obvious in the light of these facts.

Table III. shows the number of nucleated corpuscles per cubic millimetre in thirty of the cases examined by the writer.

TABLE III.—Number of Nucleated Red Cells per Cubic Millimetre in Thirty Cases of Pernicious Anæmia.

Case Number.	Total nucleated red cells.	Megaloblasts.	Normoblasts.	Microblasts.
4	7,100	5,300	1,325	475
2	6,468	3,476	924	2,068
3	854	574	266	14
4	277	277	0	0
5	240	160	80	
6	229	123	106	
7	208	130	78	
8	200	134	66	
9	117	103	14	
10	116	80	36 .	
11	114	95	19	
12	112	96	16	
13	96	96	0	
14	96	84	12	
15	92	59	33	
16	46	26	20	
17	45	36	9	
18	39	33	6	
19	35	32	3	
20	28	26	2	
21	28	21	7	
22	28	28	0	
23	18	12	6	
24	14	14	0	
25	11	11	0	
26	11	10	1	
27	11	9	2	
28	9	6	3	
29	8 3	7	1	
30	3	2	1	

## 3. White Corpuscles.

Unless the cover-glasses are spread unusually thickly, it may take a long time to find enough leucocytes for an accurate differential count, so great is the leucopenia in many cases. It is worth while, therefore, to spread some cover-glasses more thickly than would be advisable if we had only the red cells to examine. Such preparations should be dried at once by artificial heat.

TABLE IV.—PERCENTAGES OF LEUCOCYTES IN PERNICIOUS ANÆMIA.

Lymphocytes, Larg	E AND SMALL.	Eosinoph	ILES.	
No.	Per cent.	No.	Per cent.	counts.
No.  1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 24 25 26 27 28 29 30		No.  1		Number of counts.  1 1 1 2 2 3 1 1 1 5 1 2 1 1 5 1 2 1 1 5 1 2 1 1 1 2 1 1 1 2 1 1 1 2 1 1 1 1
31 32 33 34 35 36	36.1 35.7 35.6 35.6 34.	31 32 33 34 35 36	1.5 1.4 1.2 1.2	1 1 3 1 1

TABLE IV.—PERCENTAGE	OF LEUCOCYTES IN	PERNICIOUS ANÆMIA
	(Continued).	

LYMPHOCYTES, LARGE AND SMALL.		Eosinophiles.		Number of
No.	Per cent.	No.	Per cent.	counts.
37	33.6	37	1.	1
8	33.1	38	1.	2
9	33.	39	1.	1
0	33.	40	.8	1
1	31.8	41	.8	1
2	29.4	42	.8	ī
3	28.7	43	.7	ll ī
4	28.4	44	. 6	l ī
5	27.3	45	.5	1
6	27.2	46	?	1
7	26.5	47	.3	1
8	24.2	48	.2	2
9	22.	49	.0	1
0	21.2	50	.0	l ī
1	19.8	51	.0	1
2	16.	52	.0	

The essential point shown in these tables is the absolute and relative diminution in the polynuclear cells which corresponds with a percentage increase in the other forms. Absolutely the lymphocytes are about normal.

In 52 cases examined by myself the lymphocytes (large and small) averaged 45.4 per cent. About nine-tenths of these were small forms. As the fatal termination approaches, the percentage of lymphocytes rises. An extreme case of this change has already been recorded on page 103. Two other cases showed respectively 71 and 79 per cent of lymphocytes a few days before death. The polymorphonuclear cells suffer proportionately as a rule. On the other hand, Ewing has observed a marked rise in the percentage of the polynuclear cells near death, although autopsy revealed no complication. Pneumonia or septic complications may produce an ordinary polynuclear leucocytosis.

Eosinophiles are occasionally increased, 9 per cent being present in one of my cases, 6.6 per cent in another. The average of 78 examinations in my 52 cases is 2.7 per cent.

Small percentages of *myelocytes* are the rule. They are present in 42 of 52 cases. Table V. shows the percentages.

As has been explained above (page 119), the myelocyte is found in a great variety of affections, although very sparingly in most,

TABLE V.

No.	Percentage of myelocytes.	No.	Percentage of myelocytes.	No.	Percentage of myelocytes.
1	9.2	19	1.8	37	0.6
2	8.8	20	1.5	38	.6
3	8.	21	1.5	39	.5
4	6.3	22	1.5	40	.4
5	6.	23	1.4	41	.3
6	4.6	24	1.2	42	.2
7	4.	25	1.	43	.0
8	4.	26	1	44	.0
9	3.6	27	1.	45	.0
10	3.4	28	1	40	.0
11	3,	29	1	477	.0
12	3.	30	.8	40	.0
13	2.7	31	.8	40	.0
14	2.5	32	.8	=0	
	2.2	99	.6	E-4	.0
15	2.2	33			.0
16	2.2	34	.6	52	.0
17		35	.6	Average = 2 per cent.	
18	2.0	36	.6		

but, so far as my observations go, its presence is more constant and the percentages run higher in pernicious anæmia than in any other disease except leukæmia. I am speaking now of percentages. With a leucopenia such as is usually present in pernicious anæmia, 2 per cent of myelocytes means absolutely a very small number per cubic millimetre.

Taking 3,800 leucocytes per cubic millimetre as the average for pernicious anæmia (see above, page 135), 2 per cent of myelocytes amounts to only 76 per cubic millimetre. In leukæmia the absolute number of myelocytes is seldom under 150,000 per cubic millimetre.

#### The Blood in Remissions.

- 1. The Color Index. When the red corpuscles begin to increase the color index may remain relatively high or even become still higher (Laache, Schaumann); but in the majority of cases this is not so. As a rule, in the remissions of the disease the hæmoglobin is relatively low, as in ordinary symptomatic anæmia, and I have seen two cases which, if examined for the first time during the period of remission, would have certainly been mistaken for ordinary chlorosis.
- 2. The Leucocytes. Coinciding with the increase in the red cells there is usually a still greater increase in the leucocytes, so

that for a time a moderate leucocytosis may be present. This increase is made up very largely of polymorphonuclear neutrophiles, and is due, no doubt, to the increased activity of the marrow through which both red corpuscles and granular leucocytes are multiplied. The eosinophiles may also be increased as in the following case of Ehrlich: Red cells, 4,115,000; white cells, 18,300. Differential count of 400 cells showed: Polynuclears, 78.2 per cent; lymphocytes, 12; large mononuclear, 0; eosinophiles, 9.5 per cent. In another similar case he found 11 per cent of eosinophiles.

As the percentage of polymorphonuclear neutrophiles increases the percentage of lymphocytes decreases, and the myelocytes, which are usually present in small percentages during the active stages of the disease, disappear. The number of megaloblasts steadily decreases, and in their place normoblasts appear for a time; later they, too, leave the circulating blood. The size of the individual red cells is sometimes greater during a remission of the disease than at any other time. In one remarkable case the patient, whose symptoms had totally disappeared and who was actively at work as a newspaper correspondent, dropped in to see me one day, apparently in splendid health and spirits. His skin and mucous membranes were ruddy red, his hæmoglobin 90 per cent, yet to my great surprise I found only 2,500,000 red cells to the cubic millimetre. The stained specimens showed the largest red cells which I have ever seen, for the most part perfectly well shaped and natural looking, but averaging  $12 \mu$  in diameter. This stage is, however, a comparatively short one, and the size of the red corpuscles soon becomes normal or subnormal. The abnormal staining reactions and the oval forms disappear. As a rule, the count of corpuscles does not remain long above 4,000,000, but ranges in the neighborhood of 3,000,000 during the greater part of the remission.

3. The Red Cells. Usually the proportion of large forms diminishes as in Ehrlich's case: (a) Active stage; red cells 1,340,000, large forms 66 per cent. (b) Remission; red cells 4,115,000, large forms 33 per cent. At the beginning of the remission the number of megaloblasts diminishes, while the normoblasts increase. Later the latter also disappear. Deformities become less marked and the "pessary shaped" cells (pale centres) appear, giving the blood the appearance of secondary anæmia. Polychromatophilic and spotted cells grow less numerous, but Ehrlich maintains that the latter may remain even when the blood has otherwise regained

its normal appearance. He therefore considers "spotted red cells" of value for diagnosis during remissions.

The rate of regeneration is often astonishingly rapid.

In Case VII. of my series the red cells increased from 1,800,000 to 5,200,000 in fourteen days. In Case XXXIX. the red cells increased from 2,200,000 to 4,000,000 in thirteen days. In Case LVIII. the red cells increased from 1,500,000 to 3,200,000 in twelve days. In Case XCI. the red cells increased from 1,700,000 to 3,000,000 in fourteen days.

Similar observations have been reported by Ehrlich and other observers.

It is quite possible, although I have no figures to prove it, that in the periods of decline the red corpuscles may fall as rapidly as they subsequently rise. This possibility is suggested by the fact that one rarely sees pernicious anæmia in an early stage—that is, until the red corpuscles have fallen below 2,000,000 per cubic millimetre. Only four of my cases showed more than 2,000,000 red corpuscles per cubic millimetre at the time of the first examination of the blood.

### Summary.

The more important characteristics of the blood of pernicious anæmia are as follows:

- 1. Red cells about 1,200,000 per cubic millimetre.
- 2. White cells much diminished.
- 3. Hæmoglobin variable, sometimes increased relatively (= high color index).
  - 4. Deformities in size and shape of red cells in many cases.
  - 5. Increase in average diameter of red cells.
  - 6. Polychromatophilic red cells.
  - 7. Megaloblasts more numerous than normoblasts.
  - 8. Lymphocytosis.
  - 9. Small percentage of myelocytes.

The items italicized are the most important and characteristic.

# Diagnostic Value.

1. Pernicious anæmia and chlorosis may be indistinguishable without the examination of the blood. The pallor of the two diseases is not always different either in degree or in kind, and the symptoms and physical signs may be identical.

The differential diagnosis is easily made by the blood. The red cells rarely reach as low as 2,000,000 in chlorosis and the number and degree of degenerative changes are less than in pernicious anæmia. Megaloblasts have been seen in chlorosis (Hammerschlag) but have never constituted a majority of the nucleated red cells present. In the great majority of cases the pallor and other signs and symptoms of chlorosis are due to lack of hæmoglobin per corpuscle (for the corpuscles are not only pale but very small-sized), and not to a lack of corpuscles. The high color index and large size of the scanty cells in pernicious anæmia contrast strongly with this.

The white cells are about the same in both diseases, though usually fewer in pernicious anæmia. Lymphocytosis is common to both diseases. Myelocytes are occasionally found in chlorosis, but much less commonly than in pernicious anæmia.

2. Pernicious Anæmia and the Anæmia of Malignant Disease.—
Not long ago I examined the blood of a gentleman who had gradually and without assignable cause acquired a "lemon-yellow" pallor, without loss of flesh, vomiting, pain, or any localizing sign or symptom. The diagnosis of pernicious anæmia had been made. To my great surprise I found over 4,000,000 red cells, with only 38 per cent of hæmoglobin, and 18,780 white cells, 86 per cent of which were polymorphonuclear neutrophiles. One normoblast was seen. Fibrin was not increased. The anæmia was evidently secondary, and the autopsy ten months later showed cancer of the stomach.

Osler and McCrae record a case in which the symptoms and signs (except the blood) were so suggestive of pernicious anæmia that Osler made that diagnosis. Six months later a nodular mass was felt in the region of the stomach and the patient soon after died. In this case the red cells varied between 2,840,000 and 3,048,000. The leucocytes numbered 11,500; there were no nucleated red cells and but slight poikilocytosis. Hæmoglobin was 25 per cent, *i.e.*, the blood of secondary anæmia. I have since had four similar cases.

Malignant disease may bring down the count of red cells to 1,000,000 or lower, but in such cases leucocytosis is often present. As will be seen in the chapter on malignant disease, leucocytosis is by no means invariable in the anæmia of cancerous growth, but in those cases which cause such an anæmia as to resemble the counts of pernicious anæmia, leucocytosis is the rule. This in itself is

usually sufficient to exclude uncomplicated pernicious anæmia. When an increase in the whole number of leucocytes is not present in malignant disease, there is often an increased percentage of polymorphonuclear cells, contrasting strongly with the increased percentage of lymphocytes in pernicious anæmia.

Normoblasts and not megaloblasts are the rule in malignant disease. If megaloblasts are present they are in the minority, while in pernicious anæmia they are in the majority. The average size and staining-power of the red cells is increased in most cases of pernicious anæmia and decreased in most cases of malignant disease.

Ehrlich has twice diagnosed pernicious anæmia from the blood examination and been confronted at the autopsy with small cancerous growths in the stomach. In one case the cancer was "the size of a hazelnut"; in the other, "an annular fibrous cancer of the pylorus without any ulceration." In these cases I believe the cancer to have been a complication and not the cause of the anæmia. Such small growths are very rarely associated with any anæmia at all.

Hayem insists that pernicious anæmia may be distinguished from amemia secondary to cancer, because in cancer the clot contracts firmly and squeezes out the serum, and the blood plates are but slightly diminished, while in pernicious anæmia the clot does not retract and blood plates are greatly decreased.

3. Pernicious Anæmia and other Secondary Anæmias.—Most secondary anæmias which are severe enough to reduce the count of red cells below 2,000,000 follow the type of malignant disease and show leucocytosis. The great pallor and dyspnæa seen in connection with some cases of tuberculosis and nephritis rarely mean a low count of red cells, but simply a loss of hæmoglobin. I remember two cases in adjacent beds at the Massachusetts General Hospital, both with extreme yellow pallor without emaciation; one had 1,020,000 and the other 4,100,000 red cells, the hæmoglobin in each being about thirty per cent. The first was pernicious anæmia, the second nephritis.

Purpura, typhoid, lead poisoning, chronic malaria, and other diseases may reduce the red cells to a point as low as that seen in early stages of pernicious anæmia and may not be accompanied by leucocytosis; but the absence of changes most characteristic of the latter disease (a majority of megaloblasts, increased diam-

eter and color index in the red cells) serves to make the diagnosis clear.<sup>1</sup>

4. Pernicious Anamia and Leukamia.—Occasionally in infants these two diseases seem to approach very near each other and are difficult to distinguish. In infancy, as is well known, any anamia (primary or secondary) is apt to be accompanied by leucocytosis and an enlarged spleen. Further leukamia, which in adults usually causes a relatively slight anamia, affects the red cells much more strongly in infancy, and may reduce them to a number decidedly suggestive of pernicious anamia. Therefore in both diseases we may have enlarged spleen, great anamia, and leucocytosis.

The one characteristic point of leukæmic blood—the abundance of myelocytes—usually enables us to distinguish the two diseases, for although present in both diseases the myelocyte is much more plentiful in leukæmia. Unfortunately we have no way of fixing just how numerous myelocytes must be in order to constitute leukæmia. It is only in infancy and very rarely then that this difficulty arises, but at that period I am inclined to believe that we sometimes see conditions intermediate between the two diseases, indicating the ultimate identity of the two. Their numerous clinical resemblances cannot here be discussed. (For further comment on this point see page 454).

# PROGNOSTIC VALUE OF THE BLOOD IN PERNICIOUS ANÆMIA.

The prognosis is always very bad, but the following scheme indicates the presence of a severe or of a mild type:

- 1. Severe (rapidly fatal).
- (a) Extreme progressive an-
- (b) High color index.
- (c) Increase in size of red cells.
- (d) Degenerative changes.
- (e) Numerous megaloblasts.
- (f) Few or no normoblasts.
- (g) Lymphocytosis.

- 2. Less Severe (slower course).
- (a) Remissions.
- (b) Normal or low color index.
- (c) Normal-sized or small cells.
- (d) No degenerative change.
- (e) Numerous normoblasts.
- (f) Few megaloblasts.
- (g) Normal percentage of polymorphonuclear cells.

It has been thought by some observers that the absence or great

<sup>&</sup>lt;sup>1</sup> Another point of difference emphasized by Grawitz is that the plasma of pernicious anæmia has a relatively larger amount of solids than that of anæmia secondary to the above diseases. This is hardly a clinically applicable test, but is said to be a valuable one.

scantiness of nucleated corpuscles indicated lack of any effort at regeneration on the part of the blood-making functions and hence a peculiarly malignant type of the disease. I have never seen cases

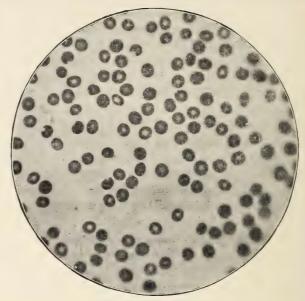


Fig. 30.-Normal Blood. Magnified 350 diameters.

in which nucleated corpuscles were steadily absent, but their scantiness has seemed to me as a rule to be associated with a more *slowly* fatal type of the disease.

No significance has seemed to me to attach to the presence of larger or smaller percentages of eosinophiles.

	Pernicious anæmia.	Chlorosis.	Secondary anæmia.
White cells	Usually decreased	Rarely under 2,000,000 Usually normal	Usually increased.
		Always relatively low	Relatively low. Rare; never more numerous than normoblasts.
Normoblasts	cells.	Occasional; always more numerous than megalo-	Common.
	Increased	blasts. Diminished	Various; not increased.
Lymphocytes Polymorphonu - clear cells.	Increased Decreased	Increased	Usually diminished. Usually increased.
	Common	Rare	Rare.

To illustrate the different size of the cells in chlorosis and pernicious anæmia I have had photographs taken of the blood of a case

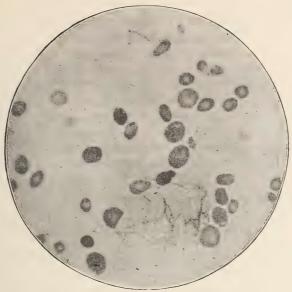


Fig. 31.—Pernicious Anæmia. Magnified 350 diameters. Note the relatively large size and well-stained centres of the cells.

of two of these diseases and of normal blood, all on precisely the same scale (see Figs. 30, 31, 32).

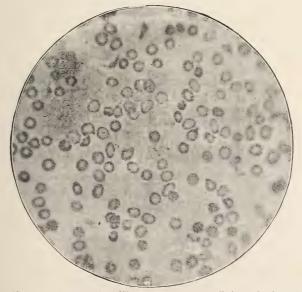


Fig. 32.—Chlorosis. Magnified 350 mameters. Note small size and pale centres.

#### 2. FATAL ANÆMIA WITH HYPOPLASTIC MARROW.

("Aplastic Anamia.")

Ehrlich reported in 1888 the case of a girl of twenty-one, with cutaneous, uterine, buccal, and retinal hemorrhages, which caused death within thirty days from the first symptom. Blood examination showed 213,360 red cells—small, fairly stained forms predominating. Deformities were slight. No nucleated red cells could be found despite many hours' search before and after death. Leucocytes numbered 200 per cubic millimetre—an astonishing leucopenia. Eighty per cent of these white cells were lymphocytes and 6 per cent large mononuclears, leaving but 14 per cent (or 28 per cubic millimetre) of polynuclear neutrophilic cells. In other words, the neutrophiles were reduced to about  $\frac{1}{170}$  of their normal number, while the lymphocytes were distinctly though less markedly diminished. Eosinophiles were wanting altogether.

The great diminution in red cells and granular leucocytes in this case suggested to Ehrlich a lack of compensatory reaction on the part of the marrow. Autopsy confirmed this. The marrow of the femur was yellow throughout except for a tinge of red near the lower end.

Similar cases have lately been reported by Lipowski  $^{2}$  and by Muir.  $^{3}$  In these as in Ehrlich's case hemorrhages were prominent.

The red cells in Muir's case were not increased in size and their number was reduced to 800,000 and the hæmoglobin to 11 per cent. The leucocytes numbered 7,000 per cubic millimetre, but only 25 per cent of them were polynuclear neutrophiles. Eosinophiles and blood plates were entirely absent. No nucleated red cells could be found in the blood, and only one or two in the marrow, post mortem, despite long and careful search. The marrow was of the fatty type, almost white, and contained few neutrophiles and no eosinophiles.

In Lipowski's case as in Ehrlich's and in Muir's the disease was dubbed "purpura hæmorrhagica" owing to the profuse hemorrhages from mucous, serous, and cutaneous surfaces. The red cells were 2,112,000, hæmoglobin was 18 per cent. Only 7 per cent of the leucocytes were neutrophiles, the rest lymphocytes. Nucleated red cells were absent.

<sup>&</sup>lt;sup>1</sup> Charité-Annalen, xiii.

<sup>&</sup>lt;sup>2</sup> Lipowski: Deut. med. Woch., 1900, p. 340.

<sup>&</sup>lt;sup>3</sup> Muir: Brit. Med. Jour., 1900, p. 910.

#### 3. THE BLOOD IN CHLOROSIS.

This has been already described for the most part under the heading of Secondary Anæmia. In many cases the two are indistinguishable by the blood examination alone, the changes consisting simply in the presence of light, small-sized, pale, more or less deformed red cells whose number may or may not be decreased, according to the severity of the case. Leucocytosis is rarely if ever present in uncomplicated chlorosis, but is often absent in secondary anæmia. Normoblasts may be present in both. The chief points of distinction are:

- (a) The red cells are more apt to be uniformly under-sized and under-colored in chlorosis, while in secondary anæmia we more often find normal cells among the diseased ones.
- (b) The color index may be lower in chlorosis than is common in secondary anæmia, and this lowering is more constant in chlorosis.
- (c) Absolute diminution in the number of polynuclear leucocytes which is very common in chlorosis, is not so common in secondary anæmia.
- (d) Nucleated corpuscles are less common in chlorosis than in anæmia secondary to malignant disease.
- (e) Coagulation is rapid, in contrast with the very slow clotting of pernicious anæmia and of many secondary anæmias. Yet fibrin is not increased. The increased rate of coagulation seems to be connected with the marked increase in blood plates, which is almost always present.

# Volume and Oxygen Capacity of the Blood.

The blood volume is greatly increased. In 21 cases with hæmoglobin below 50 per cent Smith found the average volume 4,883 c.c., or over one-half greater than the normal average (3,240). The volume is increased in proportion to the severity of the disease. Some cases showed 6,400 c.c. of blood, or nearly double the average. At the same time the total oxygen capacity (or total hæmoglobin) is approximately normal, averaging over 95 per cent in 21 cases. As the specific gravity of the plasma is normal, there appears to be a great increase in the amount of normal plasma. If we were to imagine this excess of plasma filtered off, there would remain (e.g., in Case X. of Smith's series with 6,266 c.c. and 2,600,000 red cells) about 8,000,000 red cells per cubic millimetre. Hence Smith con-

cludes that there is really a large absolute increase in the number of red and white cells disguised by an excess of plasma. Under treatment the oxygen capacity or hæmoglobin is not really increased, but the amount of plasma diminishes—in one case from 4,574 c.c. to 2,800 c.c. If confirmed Smith's results will revolutionize our ideas of chlorosis.

#### The Blood in Gross.

The pallor of the drop is sometimes excessive, fully as great as in pernicious anæmia, and the liquid is very fluid and thin. Yet it coagulates very rapidly and our technique must be prompt.

#### RED CELLS AND HÆMOGLOBIN.

### Quantitative Changes.

Hayem has recorded cases whose count was as low as 1,662,000 and even 937,360 per cubic millimetre. Such figures are certainly rare in this country, and the striking fact is usually the *slight* numerical loss of red cells, considering the extreme pallor of the patients.

The lowest count in the Massachusetts General Hospital series was 1,932,000, and in W. S. Thayer's 63 cases 1,953,000. The accompanying tables, from the Massachusetts General Hospital records, show the range of red cells and hæmoglobin in 179 cases as counted when the patients first came under observation. The highest counts (7,100,000 and 5,884,000) are undoubtedly due to some temporary stasis or concentration of the blood.

The average of the 179 cases, 4,700,000 red cells per cubic millimetre, is somewhat higher than in Thayer's' series above referred to, the average of which is 4,096,544.

The average hæmoglobin percentage of this series, 41.2 per cent, is also very close to Thayer's (42.3 per cent). This gives us on the average a reduction of the corpuscle substance to one-half the normal, or to the equivalent of 2,250,000 healthy red cells; 95 of the 179 cases have 4,000,000 or more red cells. These figures do not agree with those collected by v. Limbeck, in which only 99 out of 247 are over 4,000,000. But this probably means simply that in this country the patients seek medical advice before their disease has advanced very far, while in Germany they wait longer before

<sup>1</sup> See Osler's article on Chlorosis in the "American Text-Book of Medicine," vol. ii., 1894.

resorting to a hospital. For, as above explained, in all anemias the individual corpuscles suffer in quality first and only after some time begin to decline in number. This is especially the case in chlorosis, although by no means peculiar to that disease.

The color index is invariably low, as seen in the table, although it is rare to see it fall below .30. In only four cases of the present series did it go below that figure, the average being about .50.

v. Noorden' found that the color index was especially apt to be low in first attacks and less often in the recurrent or habitual cases, but Romberg,² in a study of one hundred and seventeen cases, has not found this true, and I agree with Romberg. One of the lowest color indexes in my series was in a woman over fifty who had a truly habitual chlorosis.

#### Table VI.—Chlorosis.

	Red Cells.								Cases.
Between	7,000,000	and	8,000,000	 	 				1
66	6,000,000	66	7,000,000	 	 				2
66	5,000,000	66	6,000,000	 	 				24
66	4,000,000	66	5,000,000	 	 				68
66	3,000,000	66	4,000,000						58
66	2,000,000	46	3,000,000						
44	1,000,000	66	2,000,000						

Average of these 179 cases = 4,700,000

		White	ells.		(	Cases.	1	White	cells		Cases.
26,	000					1	Between	7,000	and	6,000	. 29
Be	tween	15,000	and	14,000		4	66	6,000	66	5,000	18
		14,000	46	13,000		2	66	5,000	46	4,000	. 15
	66	13,000	66	12,000		8	"	4,000	66	3,000	. 10
	44	12,000	66	11,000		11	44	3,000	66	2,000	. 2
	44	11,000	66	10,000		14	44	2,000	66	1,000	. 2
	44	10,000	66	9,000		12					
	44	9,000	66	8,000		9					168
	66	8,000	66	7,000		31		Av	erag	e, 8,000	

PER CENT OF HÆMOGLOBIN IN CHLOROSIS.

Average, 41 per cent.

<sup>1 &</sup>quot;Chlorosis," Wien, 1897 (Hölder).2 Berl. klin. Woch., June 28th, 1897.

The striking contrast is with pernicious anæmia, rather than with secondary anæmia. In the former the color index, as above mentioned, averaged 1.04 in 68 cases. In secondary anæmia it is almost always below 1, but does not average so low as in chlorosis, although in individual cases it may be very low.

For example, Osterspey quotes a case of gastric cancer with a blood count of 4,230,000 red cells, and only 22 per cent of hæmogobin, a color index of .26.

### Qualitative Changes.

- (a) The stained specimen shows a greater or less degree of pallor of the corpuscle centres corresponding so accurately to the diminution in hæmoglobin that a practised observer can tell approximately how low it is simply from the stained specimen. The pallor, however, is to be taken in connection with the size of the cells, for the diminution in hæmoglobin is not due simply to a bleaching out of the cells, but to their loss of size. Hence,
- (b) The diminution in the average diameter of the cells is a very important feature. In the convalescent we may watch the gradual increase in the average diameter of the cells from  $5.5~\mu$  or lower up to  $7.9~\mu$  or even  $8.2~\mu$  (see Appendix C). Both in this respect and as regards the bleaching of individual cells, many cases contrast with most secondary anæmias, in that a large proportion of the cells are affected alike, i.e., are small and pale, while in secondary anæmia there are apt to be well-stained and good-sized or over-sized cells in every field. These last occur also in chlorosis, but less frequently as a rule. Hence the usually lower color index of chlorosis. In certain cases this distinction does not hold, and the two conditions are identical in so far as the size and color of the red cells are concerned.
- (c) Deformities in size and shape are very common in all advanced cases, but often absent in mild or moderate ones. They present no special peculiarities except that macrocytes are relatively rare and microcytes relatively common. In the severest cases, however, the macrocytes begin to get more numerous and we approach the picture of pernicious anæmia.
- (d) Degenerative changes (Maragliano, see page 86) are not common but are occasionally present in severe cases.
- (e) Nucleated red corpuscles are very scanty even in advanced cases. Hayem never saw any, but most observers find them in

small numbers after long search. They are almost always of the normoblast type, but megaloblasts have also been found. In four cases of my series normoblasts in small numbers have been found—never more than one hundred and twelve per cubic millimetre. I have never found megaloblasts.

The scantiness of nucleated red cells is a point of contrast with the anæmia secondary to malignant disease, in which even in mildly anæmic states we readily find nucleated corpuscles, while in chlorosis, even in severe cases, a long search may show very few or even none at all.

# Specific Gravity.

Chlorosis is usually agreed to be one of the diseases in which specific gravity and hæmoglobin run parallel, and as the inaccuracies and inconveniences of the v. Fleischl instrument are so great, it seems to the writer better to follow the specific gravity rather than the hæmoglobin. The tables on page 41 (Part I.) show how the inference from density to coloring matter can be made. A specific gravity of 1030 is not very rare.

#### WHITE CELLS.

# A. Quantitative Changes.

Leucocytosis is absent in uncomplicated cases. In the series in Table VI. the occasional leucocytosis may be due to digestive or to a variety of other influences (uterine troubles, etc.), which could not be excluded.

The average in Thayer's 63 cases was 8,467; in the present series (see Table VI.) it is just under 8,000.

As in pernicious anæmia, the worst cases are apt to have leucopenia, and as improvement progresses the white rise even faster than the red corpuscles.

Thus in Romberg's careful study of 117 cases, 24 cases whose hæmoglobin was under 40 per cent had an average of 6,350 leucocytes per cubic millimetre, while 52 cases whose hæmoglobin averaged 60 per cent had an average of 9,250 leucocytes. He found the average in healthy girls of the same age to be 9,068 white cells per cubic millimetre.

The absence of leucocytosis is the most important point in dis-

.

tinguishing chlorosis from secondary anæmia due to cancer, suppuration, etc.

# B. Qualitative Changes.

Lymphocytosis is usually present, as in pernicious anæmia, whenever the disease is well marked, and sometimes even in mild cases. Thus Rieder found in 12 cases an average of 33 per cent of lymphocytes, the highest percentages being 53.7, 43.5, and 41.7. Either the small or the large lymphocytes may predominate. In my own experience it has usually been the small forms.

The neutrophiles suffer proportionally, their low percentage contrasting often with that of secondary anæmia associated with leucocytosis. Eosinophiles are occasionally increased. In Rieder's 12 cases the average percentage was 3.5, the highest percentages being 9.6 and 7 per cent.

Myelocytes are rare but have occasionally been observed in small numbers.

# Regeneration of the Blood.

As the patients begin to mend under the influence of treatment, the blood changes are just the reverse of those seen during the development of the disease. First the corpuscles gain in numbers, the hæmoglobin still remaining low; later and much more slowly the coloring matter, size, and weight of the cells are renewed. It seems as if the new-formed cells were of light weight and had to be replaced gradually by cells of normal stature. The nucleated corpuscles and deformities disappear and the leucocytes shoot up often a little above the normal.

#### Blood Plates.

They are usually considerably increased.

# Chlorosis without Known Blood Changes.

Romberg quotes the following facts: Three girls, nineteen, twenty, and twenty-five years of age, came to him with typical symptoms of chlorosis. Their blood counts showed:

I. Red cells, 5,246,000; Hb., 80 per cent.

II. " " 5,376,000; " 83 "

III. " " 4,408,000; " 87 "

All improved markedly under iron treatment.

I mention this because I have seen several similar cases and have heard of others from colleagues.

### Summary.

- 1. Blood as a whole: Very pale in marked cases, very fluid, but coagulates rapidly. Fibrin not increased. Specific gravity usually low, running parallel with the hæmoglobin.
- 2. Red cells: Average 4,000,000 the when patient is first seen, very rarely go below 1,000,000. The majority of them are *small-sized*, *pale*, often deformed. Nucleated corpuscles are rare (normoblasts as a rule).
  - 3. White cells not increased.

Lymphocytosis, occasionally eosinophilia.

4. Blood plates increased.

### Diagnostic Value.

- 1. The points of difference from pernicious anæmia have been discussed.
- 2. It is important to distinguish it from simple debility, and from cases in which the skin only is anæmic; in both of these conditions the blood is normal.
- 3. From secondary anaemia it may be indistinguishable in case the latter be without leucocytosis. When leucocytosis is constantly present and the percentage of polymorphonuclear leucocytes is increased, chlorosis (uncomplicated) can be excluded. Of course many of the complications which may occur in chlorosis are accompanied by leucocytosis.

### CHAPTER II.

#### LEUKÆMIA.

The distinction between leukæmia and leucocytosis has been sufficiently dwelt on above.

The blood of the vast majority of cases of leukæmia falls clearly under one or the other of two distinct types, myeloid on the one hand, lymphoid on the other. Myeloid blood is found only in cases with great hypertrophy of the spleen, marked marrow changes, and little or no enlargement of the other lymphatic tissue. Such cases are usually chronic (two to five years). Lymphoid blood, on the other hand, may be associated either with acute or chronic forms of the disease, and while in all cases we have some set of lymphatic glands enlarged there may be no externally visible glands enlarged, and the spleen may be as big as in cases of the myeloid type. The diagnosis of leukæmia can easily be made by the blood alone, but we cannot say from the blood whether or not the spleen or the visible lymph glands are hypertrophied. In acute cases the lymph glands of the alimentary tract (cervical, faucial, gastroenteric, mesenteric) may be the only set involved.

All of the thirty-seven cases associated with myeloid blood which have come under my observation have run a chronic course, while of the cases showing lymphæmia seven were chronic, five acute, and five subacute. All the myeloid cases had very large spleens without enlargement of visible lymph glands, but three of the lymphatic cases had spleens almost filling the abdomen.

The disease leukæmia, then, is associated with two types of blood.

- 1. Myeloid blood.
- 2. Lymphoid blood.

#### I. MYELOID LEUKÆMIA.

The drop as it emerges from the puncture looks somewhat opaque in color, but is neither whitish nor chocolate colored. It flows very sluggishly, however, and is difficult to spread between cover-glasses owing to the masses of white cells contained in it. Coagulation is normal, three minutes or less with Wright's coagulometer, and fibrin is not increased.

#### RED CELLS.

In the earlier stages of the disease there is no anæmia. Later the diminution in red cells is moderate, averaging about 3,120,000 in the forty-seven cases of Table VII. Toward the end of life the count of red cells often falls below 2,000,000. The patients are often not pale and may feel perfectly well. The hæmoglobin is usually diminished, the color index being about 0.6 in my cases. It is difficult to read the v. Fleischl instrument in leukæmia, as the presence of so many leucocytes gives a muddy tint to the liquid, not easy to compare with the red of the glass.

TABLE VII.—LEUKÆMIA.

No.		Red cells.	No.		White cells
1	Highest.	5,000,000	1	Highest.	1,072,222
2		4,877,000	2		980,000
3		4,800,000	3		820,000
4		4,592,000	4		800,000
5		4,288,000	5		756,000
6		4,140,000	6		748,000
7		4,016,000	7		716,000
8		3,760,000	8		656,000
9		3,635,570	9		626,600
10		3,605,000	10		570,000
[1		3,400,000	11		500,000
12	0	3,292,000	12		492,000
13		3,200,000	13		454,000
14		3,170,000	14		453,000
15		3,090,000	15		448,000
16		3,080,000	16		430,000
17		3,020,000	17		428,000
18		3,078,000	18		405,000
19		3,010,000	19		400,000
20		2,996,000	20		394,000
21		2,960,000	21		386,000
22		2,952,000	22		367,000
23		2,938,000	23		340,000

TABLE VII.—LEUKÆMIA (Continued).

No.	Red cells.	No.	White cells
24	. 2,921,600	24	324,000
$25.\ldots$	. 2,868,000	25	900,000
26	. 2,792,000	26	290,000
27	. 2,738,000	27	290,000
28	. 2,715,000	28	260,000
29	. 2,706,000	29	260,000
30	. 2,576,000	30	248,000
31	. 2,520,000	31	220 200
32	2,500,000	32	0 1 0 0 0 0
33	. 2,322,222	33	1 400,000
84	. 2,320,000	34	186,000
35	0.000.000	35	100,000
36	2,140,000	36	
37	2,112,000	37	170,000
38	. 2,060,000	38	141,000
39	. 2,016,000	39	139,600
10	. 2,010,000	40	138,000
11	. 1,866,664	41	134,400
[2	. 1,756,000	42	132,000
13	. 1,420,000	43	111,000
4	. 1,386,000	44 Lowest	98,000
5	. 1,358,000		
6	. 1,200,000	Avera	ge = 428,000
7 Lowest	408,000		
A Trans ma	= 3,131,000+		

### Qualitative Changes.

The striking point is the presence of very numerous nucleated red cells, even in the absence of any sign of anæmia. With over 4,000,000 well-formed and well-colored red cells, we may have hundreds of erythroblasts in every cover-glass. They are as numerous in this form of leukæmia as in the worst forms of pernicious anæmia, even though the patient may be feeling nearly well. In Taylor's cases there were ten with 10,000 or less of the nucleated red cells per cubic millimetre, three with 10,000 to 20,000, and two between 60,000 and 70,000. One showed only 360 per cubic millimetre.

Both normoblasts and megaloblasts may be seen, but in most cases the latter are in the minority. Many of the normoblasts show fragmentation in their nuclei, and occasionally true karyokinetic figures are seen. In the anemic cases we find all the other changes in the red cells characteristic of anemia, but the nucleated cells are almost always more prominent than in any other form of anemia of a like severity. This shows that nucleated corpuscles



#### PLATE II.

Fig. 1.—Both this and Fig. 2 are intended to be fac-similes of actual microscopic fields.

(a) Note the cell between those labelled 8 and 9—apparently a "mast cell." Such cells are often seen in this form of leukæmia. With Ehrlich's stain they present this appearance. Basic stains bring out coarse blue granules in the periphery of the protoplasm.

(b) Note also the cell at the extreme upper right-hand corner of Fig. 1, which it is almost impossible to classify either as a myelocyte or as a polymorphonuclear neutrophile, since it appears to be intermediate between the two varieties.

(c) Both the nucleated corpuscles are normoblasts; 9 has polychromatophilic protoplasm. The red cells show scarcely any deformities and very slight deficiency in coloring matter.

Fig. 2.—(a) Note the deformities in size and shape of red corpuscles, owing to the ansemia present.

(b) No lymphocytes are figured, as they made up only two per cent of the white cells in this case. Eosinophiles were absent.

(c) Note that the contrast between this figure (leucocytosis) and the one above it (leukæmia) is not in the abundance of white cells but in the kind of white cell predominating among those present.

## Examination of the Blood.

#### PLATE II.

Figure I = Splenic-myelogenous Leucaemia

Figure II = Leucocytosis (cancer of kidney)

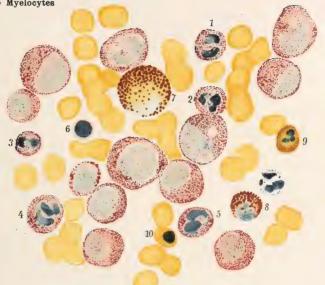
Cells stained yellow = Red corpuscles

1. 2. 3. 4 a. 5 = Polymorphonuclear neutrophiles

6 = Lymphocyte 7 a. 8. = Eosinophiles

9 a. 10 = Nucleated red corpuscles

All others = Myelocytes



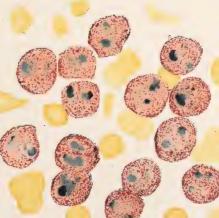
Cells stained yellow = Red corpuscles
All others =

Polymorphonuclear-

Figure I Leucaemia.

nuclearneutrophiles





Scale of µ



are not to be thought of as evidence (like deformities in shape) of regenerative or degenerative conditions only. A special connection to the wide circulatory channels of leukæmic marrow is very clearly indicated, all the more so as in the lymphatic form of the disease in which the bone marrow is much less affected, nucleated corpuscles are much less numerous, appearing in relatively small numbers in the very acute anæmic cases and not at all in those which are not anæmic. The protoplasm of the erythroblasts is usually polychromatophilic, contrasting in this respect with the acidophilic protoplasm of embryonic and infantile erythroblasts.

The variations in size and shape correspond to the degree of anæmia present; occasionally, *i.e.*, in cases seen early in the course of the disease, the red cells are quite normal.

As the count of the white cells rises, that of the red may fall, and *vice versa*; or the red cells may remain at a comparatively high figure despite the progress of the white.

#### WHITE CELLS.

### Quantitative Changes.

The average number per cubic millimetre in the forty-four cases of Table VII. (the lymphatic cases being excluded) was 438,000 at the time when the cases first came under observation. The highest count in this series is 1,072,222 and the lowest 98,000.

Among the older recorded cases are some in which the white cells were said to be more numerous than the red. The average ratio in my series is about one white to seven red. The highest ratio is 1:2, and the lowest 1:37. It is best to use the "red counter" with a dilution of 1:200 in counting the white cells, otherwise they are often too crowded for convenience. Hayek has shown that the count of leucocytes may vary enormously in a very few hours; e.g, 10 a.m., 122,500; 4 p.m., 235,000; or again, 10 a.m., 730,000; 4 p.m., 547,500.

In the fresh specimen we notice that a large proportion of the white cells are but slightly amæboid, a point of marked contrast with leucocytosis, in which the leucocytes are actively amæboid. This is due to the fact that the myelocytes which form so large a portion of the leucocytes in this disease possess little power of amæboid motion.

<sup>&</sup>lt;sup>1</sup> Hayek: Wien. klin. Woch., 1897, No. 20.

TABLE VIII.-MYELOID LEUKÆMIA.

	,	1							11		
				F	PERCEN	TAGE			hile	nile	
No.	Red cells.	White cells.	Hæmoglobin. Polymorphonuclear neutrophiles.	Small lymphocytes.	Eosinophiles.	Myelocytes.	Basophiles.	Transitional neutrophiles.	Nomoblasts seen while counting them.	Megablasts seen while counting them.	Date.
1	2,010,000 1,720,000	716,000 732,000	30 40.0	1.0 10	0.0 4.0	42.0	3.8	Many	Many	Many	Nov. 1st, 1897.1 Nov. 3d, 1897.
.2	4,125,000	708,000 253,900	55								Nov. 12th, 1897.
,	4,016,000	200,000	56.5	7 4		28 33.5	Many	Many	3 2 3	1	July 25th, 1895. Jan. 21st, 1897.
-3	4,592,000 2,960,000	448,000 175,800	60 46 46.6 42 17	$\begin{array}{c c} 1.5 & 14 \\ 1.4 & 10 \\ 3 & 11 \end{array}$	0.4 2.2	36.7 49	66	"	3 13	$\begin{array}{c} 0 \\ 0 \\ 31 \end{array}$	July 25th, 1895. Jan. 21st, 1897. Feb. 8th, 1897. Feb. 17th, 1897. July 15th, 1897. July 29th, 1897.
.9	3,184,000 3,156,000	264,000 276,000	38								July 29th, 1897. Aug. 5th, 1897.
4 5	3.400.000	111,000 183,090	35 27.2 31	$\begin{vmatrix} 10.5 & 26 \\ 15 & 8 \end{vmatrix}$	3 5	25 32	Many	Many			,
6 7	3,670,000 3,100,000 3,080,000 2,520,000	430,000 405,000 510,000	$\begin{array}{c} 48 \\ 40 \\ 72.2 \\ 50 \\ 51 \end{array}$	$\stackrel{\cdot}{2}_{.6}$	6 2	17.4 42.4	Many	Many	5	9	Aug. 10th, 1896. Aug. 31st, 1896. Jan. 22d, 1896.
1	2,520,000	528,000 570,000	30 31			12.1					Jan. 22d, 1896. <sup>2</sup> Jan. 23d, 1896. <sup>2</sup>
8	4,016,000	560,000 800,000	58 55	5 4		94	Many	Many			Aug. 318t, 1396. Jan. 22d, 1896. Jan. 22d, 1896. <sup>2</sup> Jan. 23d, 1896. Jan. 24th, 1896. June 4th, 1894. Aug. 10th, 1894. April, 1893. Later
9 10	2,792,000 2,715,000	26,000 139,600 394,000	50.4	18.9 1.5 1	.2 6.1	24.4 51 30.3				• • • • • •	Aug. 10th, 1894. April, 1893. Later the count of
11 12	2,256,000 4,288,000	340,000 213,000	62.3 37 53.8	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c c} 2.5 \\ 1.8 \\ 14.4 \\ 3 \end{array}$	$\frac{30.3}{18}$	8.8				leucocytes was normal for sev-
13 14 15	2,921,600 3,010,000	492,800 188,000	61	23 + 6	8	26					eral months.
15 16	2,996,000 4,800,000 3,060,000	134,400 220,500 274,000	46 62 41 33	1.5 1	$\begin{vmatrix} .5 & 4 \\ 2.5 \\ .5 & 3 \end{vmatrix}$	48 33 42.5					Jan. 22d, 1896. June, 1897.
17 18	2,016,000 2,576,000	260,000 748,000	26	8 1	$\begin{array}{c c} .5 & 5 \\ .5 & 1.5 \end{array}$	60					June, 1001.
19	2,448,000 2,120,000	168,800 190,000	42 45	3 3	3	46					
20	2,528,000 5,120,000	188,600 159,000 134,000	$\frac{45}{78}$ $74.2$	4 4	2.8	15			4	1	Feb. 22d, 1896.
20	5,000,000 4,800,000	137,800 138,000		6 2		28					Feb. 25th, 1896. Feb. 28th, 1896.
21	4.140.000	$141,000 \\ 410,000$	61 53 58 35 48	$\frac{3}{17}$ $\frac{1}{2}$	31	35 28	$\begin{bmatrix} 0 \\ 2 \\ 2 \end{bmatrix}$		4	2 1 5	
22 23 24	2,825,000 2,175,000 2,952,000	441,000 324,000	36 43 40 33	2 18 5 5 1.2 3	$\begin{bmatrix} 7 \\ 7 \\ 4.2 \\ .6 \end{bmatrix}$	$\frac{28}{21}$	14	15	6		5.4 per cent. of the
24	3,090,000	186,000 454,000	38 57 45 47	2 2	.6 .2	48	5.2		8 1	0	lymphocytes have the char- acteristics of
0.5	2 170 000	960 000	95 41	9 0 1	.2 8.8	12	9.4			0	Türck's "Reizungsformen."
25 26	3,170,000 2,706,000	260,000 317,000 290,000	35 41 40 53 31 27	1.8 1	$\begin{array}{c c} .4 & 8.2 \\ 1.8 & 1.8 \\ \end{array}$	33 40	$\begin{bmatrix} 2.4 \\ 2.6 \\ 15 \end{bmatrix}$		1	$\frac{0}{2}$	Oct. 21st.
20	2,002,000	260,000   278,000	31 27 31 24 35 33	$\frac{3.8}{4.4}$ $\frac{12}{12}$	1.2	45	14 11		$\begin{bmatrix} 1\\2\\4 \end{bmatrix}$	2 3 4	Oct. 21st. Nov. 3d. Nov. 19th.
	2,631,000		31				1				

 $<sup>^{\</sup>rm 1}\,\rm Many$  cells on border-line between large lymphocytes and myelocytes and between these and polymorphonuclear neutrophiles.

<sup>&</sup>lt;sup>2</sup> Cerebral hemorrhage. Death January 25th, 1896.

					PEF	CEN	TAGE			while n.	ille	
No.	Red cells.	White cells.	Hæmoglobin. Polymorphonuclear neutrophiles.	Small lymphocytes.	Large lymphocytes.	Eosinophiles.	Myelocytes	Basophiles.	Transitional neutrophiles.	Normoblasts seen wheelen.	Megablasts seen while counting them.	Date.
27	1,756,000	347,900 418,000	23 35 41	3 2	5 6	2 2	54 48	0 0		2 11	3 4	First day. Phthisis also
28 29 30	2,500,000	248,000	27 32 49.6	2 4 3.6	$0 \\ 4 \\ 2.2 \\ 5$	9 5 6 5	23 55 38.6	45	25	4	2	fourth day. Türck's "Reizungsformen" 9.5 per cent.
31 32 33			1130	$\frac{10}{8}$ $24.5$	5 0 5	5 5 1 5	45 34 27.5 28 36	10				
28 29 30 31 32 33 34 35 36			36 57.5 42	4	$\frac{4}{1.5}$	28 3.7 1	28 36 47	$\frac{1.5}{2}$				

TABLE VIII.—MYELOID LEUKÆMIA (Continued).

With or without the influence of therapeutic agencies or after splenectomy the white cells may fall gradually to normal and remain there for some time. The patient's symptoms may simultaneously ameliorate, or there may be no improvement but rather the reverse. Such a case occurred under my observation, and the patient, a washerwoman, went back to work and afterward passed through an attack of lobar pneumonia in safety.

4.6 5.1 35

Av. 3,120,000 348,000 52 46

At such a time, when no increase in the white cells is present, we should never suspect leukæmia, seeing the case for the first time, unless we chance to make a differential count; then the characteristic qualitative changes (see below) may be found, or the blood may be wholly non-leukæmic, as in a case recently reported by McCrae, and in a similar case slides from which were recently shown me by Martin.

# QUALITATIVE CHANGES.

# 1. Myelocytes.

The enormous number of myelocytes is the chief point of interest. The average in my 36 cases was 35 per cent (see Table VIII.), rising in one case as high as 55 per cent and only thrice falling lower than 20 per cent.

Taking the average total number of leucocytes as 348,000 per cubic millimetre, the absolute number of myelocytes averages over 120,000 per cubic millimetre. So far as I am aware the highest count of myelocytes in any other disease is that mentioned on page 393 in a case of malignant disease, namely, 4,514 per cubic millimetre. The contrast is sufficiently striking. I wish to insist upon this point, namely, that the blood of myeloid leukæmia is absolutely peculiar and characteristic, and could not possibly be confused with that of any other disease. Certain writers of late years have concluded that because myelocytes do occur in a great variety of diseases other than leukæmia, therefore there is nothing peculiar about the blood of the latter affection. It would be as logical to say that because albumin and casts occur occasionally in the urine of persons practically well, therefore there is nothing characteristic about the urine of acute nephritis.

At the first glance the stained specimen of leukæmic blood seems to be composed mostly of myelocytes, but this is because they are on the average so much larger than the other forms of white cells, which, being packed away in the interstices between the large myelocytes, do not appear prominently at first sight.

Although (as just mentioned) the average size of the myelocytes is greater than that of any other kind of leucocyte, there is a great range of variation in their size, and some are hardly, if at all, larger than a red cell. (This is equally true of the myelocytes as seen in the bone marrow. See above, page 71.)

The individual characteristics and variations in the myelocytes have been already sufficiently described on page 69.

# 2. Polymorphonuclear Cells.

Absolutely the number of these cells is greatly increased, although the number in each 1,000 leucocytes is considerably diminished. The actual number per cubic millimetre averages over 200,000 in my series, and in all but one of Taylor's 17 there were 65,000 or more. The average percentage in the thirty-six cases of Table VIII. is 46, the figures ranging between 17 and 72 per cent.

The individual cells show a much greater range of variation in size, staining properties, and the size and shape of the nucleus than in any other condition. In most forms of leucocytosis, for example,

<sup>&</sup>lt;sup>1</sup> Taylor reports a gastric cancer with 4,285 per cubic millimetre.

one polynuclear cell looks very much like another, but in this form of leukæmia we are often struck by—

- (a) Very small cells or very large cells (4  $\mu$  to 20  $\mu$  in diameter).
- (b) Dark stained or very pale stained cells.
- (c) Unusual shapes in the nuclei.
- (d) Variations in the size and staining of the granules. While normal polynuclear cells have granules nearly of one shade, the leukæmic polynuclear cells have granules varying from yellow or pink to purple or blue. Their size also varies greatly. Taylor found some as large as eosinophilic granules.

Besides these variations we often see cells apparently belonging to this type, but whose protoplasm shows no color or granulation whatever. Other cells show a few granules scattered about against a perfectly white background. Such cells may contain basophile granules beside the neutrophile.

(e) There are always some cells on the border-line between the polymorphonuclear and the myelocyte, and in regard to which decision must be arbitrary. I have lately been in the habit of classifying such cells as *Transitional Neutrophiles*. Similar cells are found in leucocytotic and anæmic blood (see page 110).

# 3. Lymphocytes.

In percentages the lymphocytes are reduced from their normal, 20 to 30 per cent, to an average of 10.6 per cent, as in leucocytosis. But still if we class together large and small forms, their absolute number is always increased. Thus the lowest percentage present in Table VIII. (namely, two per cent) would mean 8,760 out of the average 438,000, the total leucocyte count per cubic millimetre, and 8,760 is three or four times as many lymphocytes per cubic millimetre as are present in normal blood.

The proportion of large and small forms among the lymphocytes varies a great deal. Sometimes the small lymphocytes in this form of leukæmia do not differ from those of normal blood either in absolute number or in type, but in most cases we find large numbers of the following atypical varieties:

(a) Large lymphocytes with a protoplasm so darkly stained that it is difficult to distinguish them from myelocytes. Indeed in some cases when hints of a granular look appear in the violet-stained rim we find it impossible to be sure whether we are dealing with a large lymphocyte or a myelocyte. The personal equation alone de-

cides. These cells are not peculiar to leukæmia. Türck has described them (under the name of "Reizungsformen") in most infectious diseases, and I have often seen them in the blood of malignant disease and of pernicious anæmia. Taylor and Weil class them as myelocytes without granules.

(b) Cells like lymphocytes except that they contain from three to ten widely separated granules of one or more varieties (basophilic, acidophilic, or neutrophilic).

### 4. Eosinophiles.

Like all the other varieties these are absolutely much increased. Relatively—by percentages—they may or may not be so. In my series they ranged from 1 to 19 per cent, averaging 5.1 per cent, a slight increase over the normal.

Many writers, wrongly interpreting Ehrlich's observations on this point, have stated that an increased *percentage* of eosinophilic cells was the distinguishing mark of leukæmia, and even recent writers (e.g., Gilbert, Strümpell) continue to repeat this false statement.

The cell most characteristic of splenic-myelogenous leukæmia is not the eosinophile but the myelocyte. Nevertheless eosinophiles are enormously increased absolutely and this fact may be of great diagnostic value. In a case of cancer of the marrow with anæmia and leucocytosis Epstein¹ found large numbers of myelocytes and nucleated red cells but no eosinophiles. The absence of eosinophiles in this case sufficed to exclude leukæmia.

We distinguish several types of eosinophiles in leukæmic blood.

- (a) Ordinary (polymorphonuclear) eosinophiles.
- (b) Eosinophilic dwarf cells and giant eosinophiles. In some of these the granules are also huge—even 2  $\mu$  in diameter (Taylor).
  - (c) Eosinophilic myelocytes.
- (a) Needs no comment; (b) is simply a very small cell with eosinophilic granules; sometimes such cells are not over 5  $\mu$  in diameter. They are not uncommon in this form of leukæmia and are very rare in any other disease. The same is true of (c), the eosinophilic myelocytes which are very rare in any other disease, except pernicious anæmia, in which they are occasionally seen.

These cells are like myelocytes except that their granules are eosinophilic instead of neutrophilic (see Plates I. and II.). They

'Epstein: Zeit. f. klin. Med., 1896, vol. xxx.

are found in the marrow in considerable numbers and may constitute the majority of the eosinophilic cells in this form of leukæmia. Occasionally we see eosinophiles with a few basophilic or neutrophilic granules as well. Eosinophilic myelocytes are of constant occurrence and great diagnostic value in leukæmia. In no other disease are they equally numerous. Their size, like that of the neutrophilic myelocytes, varies from 8 to  $25\,\mu$  diameter.

### 5. Basophiles.

- (a) The lymphocytes may contain basophilic granules as in any ordinary blood.
- (b) The basophilic or amphoteric tendency of the granules of some of the myelocytes has been already described (p. 69).
- (c) "Masteellen" or coarsely granular basophiles, usually with a trilobed nucleus, are almost always to be seen in specimens stained with thionin or methylene blue. With the triple stain their protoplasm is nearly unstained, but usually a number of round white spots can be made out against a faintly stained background. These are the basophilic granulations. Mast cells make up from one to ten per cent of the leucocytes in most cases of myelocytæmia. Ehrlich states that they are always present and greatly increased in such cases, but my experience and that of Taylor do not confirm this. In 2 of Taylor's 11 cases mast cells were absent. On the other hand, one of his cases showed over 140,000 mast cells per cubic millimetre (10 per cent), and it is undoubtedly true that "an excess of mast cells is one of the most trustworthy signs of myelogenous leukæmia." Their granules are not purely basic but metachromic.

#### 6. Mitoses.

Leucocytes showing mitosis are very rarely found in leukæmic blood and play a negligible part in the increase of the circulating leucocytes. They have no value in diagnosis.

# 7. Polymorphous Condition of the Blood.

Weiss has rightly insisted on the fact that in this type of leukæmia the blood preparations show a very *polymorphous* condition. There are no fixed types, but every variety shades through intermediate forms into some other variety. No two cells are

alike. Precisely the same conditions obtain in the normal marrow, and we can scarcely resist the impression that in this form of leukæmia we see in the blood unfinished cells of various kinds which usually do not appear in the circulating blood.

As Charcot-Leyden crystals have no diagnostic value and are not peculiar to any disease, no description of them will be given here. They appear to be present wherever eosinophiles are plentiful, e.g., in asthma, gonorrhea, in the bone marrow, etc.

#### 8. Remissions.

During remissions, when the leucocyte count may fall to normal, the percentage of myelocytes usually remains large and the diagnosis could thus be made even if we saw the case then for the first time. This I have observed in two cases, and Thayer and Taylor have had the same experience. But occasionally myelocytes and all other evidence of leukæmia disappear, and diagnosis in such remissions is impossible. McCrae and Martin have studied such cases.

#### II. LYMPHÆMIA.

# (Lymphatic Leukæmia.)

Although Fraenkel once maintained that all cases of lymphatic leukæmia are acute, and that therefore the difference between the various forms of the disease rests simply on the rapidity of the process in the blood and clinically, there is no doubt that chronic lymphatic leukæmia exists.

Fraenkel was enabled to maintain his position only by extending the term *acute* to cover all cases in which symptoms lasted not more than four months. Six weeks is the limit agreed upon by most other observers.

The writer has watched seven cases of typical lymphatic leukæmia for periods of from seven months to three years. In one the symptoms were very mild, and the patient came over thirty miles from time to time to report at the Out-Patient department. His blood showed little variation from the following figures: Red cells, 2,300,886; white cells, 112,000.

The differential count always showed the overwhelming majority (over ninety per cent) of small lymphocytes characteristic of the disease. The lymph glands were all much enlarged, the spleen just



#### PLATE III.

(a) Chronic Lymphæmia with Excess of Small Lymphocytes.

One polymorphonuclear cell is present. All the rest are lymphocytes and exemplify the variations in the morphology of the cell occurring in this and other diseases as well as in health, *e.g.*, variations in the staining of the protoplasm and nucleus, indentation and even division of the nucleus.

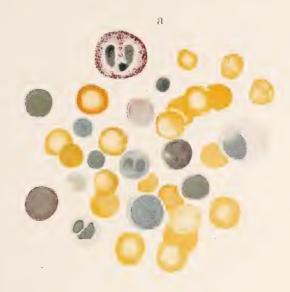
Note that the scale of the whole of Plate III. is larger than in the other plates (see scale of  $\mu$ ).

(b) Acute Lymphamia with Excess of Large Lymphocytes.

Note the lack of chromatin in both nuclei and protoplasm of large lymphocytes. The plasma around them or their extreme edge took most of the stain. The brown tint of the red cells is due to underheating. Compare the colors with those in the figure above (a) in which the preparation was properly heated.

# Examination of the Blood.

PLATE III



b



### Lymphatic Leucaemia

a. Small Lymphocytes in excess

b. Large " " "

υ 20 Scale of μ



palpable. The patient kept about his work as a gardener for over two years. Another in an active wine merchant was wholly unattended with symptoms. The patient first sought advice for the unsightly glands in his neck. He continued to feel absolutely well and to work hard until life was suddenly cut short by an attack of pneumonia. I watched his blood for three years, and it always showed typical lymphæmia without anæmia. Grawitz has watched a similar case for over four years.

The blood of acute lymphæmia differs as a rule in many cases from that of the chronic types. These differences will be referred to later on.

### RED CELLS.

The count of red cells is often somewhat lower than in the splenic-myelogenous form of the disease, averaging 3,600,000 in my cases. In acute cases it is usually very low and the anæmia progresses rapidly. In the infantile cases collected by McCrae, the highest count was 2,350,000. In chronic cases the red cells behave about as in myelocythæmia, except as regards nucleated forms.

The chief point of interest is the comparative rarity of nucleated red cells, the abundance of which is so marked a feature of splenic-myelogenous leukæmia. They may follow the grade of anæmia present. In other cases (as in one reported by McCrae) nucleated red cells are entirely absent, despite a reduction of the red cells to 1,680,000. In the eleven cases in infants collected by McCrae, there were no nucleated red cells found in seven. In acute cases the number of nucleated forms is often greater and may be as great as in myeloid leukæmia. Two cases recently reported by Herrick' exemplify this.

#### WHITE CELLS.

# $Quantitative\ Changes.$

As a rule the numerical increase is not so marked as in the splenic-myelogenous form. The average ratio of white to red cells is about 1:50 instead of 1:7, and we rarely see counts reach the height common in the other form of the disease. The highest count of my series was 1,480,000 at the patient's first visit, and the lowest 30,000, the average being 350,000 as compared with 438,000 in the myeloid leukæmia. These figures refer to uncomplicated cases.

<sup>1</sup> Journal of the American Medical Association, July 24th, 1897.

### Qualitative Changes.

1. Lymphocytes (small forms, large forms, or a mixture) make up usually over ninety per cent of all the leucocytes present. In some cases they are all nearly of one size, while in others we find every gradation from the smallest to the largest, so that it is absolutely futile to attempt to separate them into "large" and "small." Four of my cases were made up wholly of the small forms, all under  $10~\mu$  in diameter, two were composed largely of forms over  $15~\mu$  in diameter, while six showed every intermediate size.

TABLE IX.—LYMPHATIC LEUKÆMIA.

No.	Red cells.	White cells.	Per cent.	Small lymphocytes.	Large lymphocytes.	Polynuclear neutrophiles.	Eosinophiles.	Myelocytes.	Normoblasts.	Megaloblasts.	Remarks.
1 2	4,877,000 912,000 1,440,000	132,000 23,000 43,600	17 23	75.8 15.	16. 82.	4.6 2.4	1.6	2. 5	4		Subacute; ten weeks. Jan. 24th, 1896. Jan. 26th, 1896. Acute
	1,336,000 1,100,000	92,000 120,000	20	25.4	73.2	.5			3		two weeks. Jan. 27th. Jan. 28th. Death; autopsy.
3	3,000,000 3,500,000 3,608,000	31,600 31,500 28,500 40,000	55	68.5 78. 95.3	28. 15.6 **	3.2 5.6 4.3	.2				April 3d, 1896. April 5th, 1896. April 6th, 1896. April 7th, 1896. Acute;
	4,700,000 3,100,000	31,500 40,000 3,400			* 52.	4.					five weeks. April 8th, 1896. April 12th, 1896. April 22d (sepsis — semi- comatose).
4 5	2,960,000 4,160,000 2,768,000	800 1,480,000 80,000 77,500 51,800		94.7 87.9 80.5 88.7	* 12. 2.1 1.6	5.3 .1 17.2 9.4		 .1		6	April 29th. Death. March 21st, 1897. Chronic. Oct. 26th, 1896. Chronic. Nov. 5th, 1896. Nov. 7th, 1896.
e	3,520,000	79,500 64,000	60	90.4	1.4	8. 6	• • • •			• •	Nov. 15th, 1896. Nov. 17th. Died December, 1897. Chronic.
7	2,653,000	164,000	45		92.3	3.2	0	2.5	0		Positive Widal reaction, typhoid?—1,000 leucocytes counted.
8	2,477,500 4,078,000	167 500 90,200 738,000 708,000	40	98.6	*		6	 0	0	0	Second day. Third day. Death. July 21st; 500 cells counted. July 23d.
9	4,196,000 2,612,000 3,283,000	722,000 760,000 176,000 393,000	39 40		* 1.2 34. 47.	.8 .5 4.6 2.8	0 $0$ $0$ $0$	$\begin{smallmatrix}0\\.1\\0\\0\end{smallmatrix}$	$\begin{bmatrix} 0 \\ 0 \\ 1 \\ 0 \end{bmatrix}$	0	Aug. 5th; 500 cells counted. Oct.; 1,000 cells counted. Oct. 23d; 500 cells counted. Nov. 16th; 500 cells counted.
100 11	5,837,000 5,630,000	124,000 180,000 500,000		98. 97.	0 0 0	$\begin{array}{c} 6 \\ 1.9 \\ 3 \end{array}$	$0.1 \\ 0.1$	0 0	0 0	0	Nov. 24th, 1898. May 26th, 1900. Sept. 28th, 1900.
12	2,500,000	800,000		99. 99.99	0	.0001	0.2	0	0		Nov. 23d, 1900. One polynuclear in 8,000! All the rest = lymphocytes.
13	5,178,000	20,000- 60,000	95	80-90	5-8	10-15	0	0	0	0	Examined once a month for three years; excellent health throughout; died of pneumonia, Feb., 1901.

TABLE	IX.—LYMPHA	TIC LEUKÆMIA.	-Continued.
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No.	Red cells.	White cells.	Per cent hæmoglobin.	Small lymphocytes.	Large lymphocytes.	Polynuclear neutrophiles.	Eosinophiles.	Myelocytes.	Normoblasts.	Megaloblasts.	Remarks.
14 15 16 17 18 19 20 Av'age	700,000	600,000	10	94. 97.9 86.2 72. 99.6 92.2 99.8 80.2	* 7. 7. * * * * 15.	7.8	.8		2 Few.		

<sup>\*</sup> Large and small forms counted together on account of the impossibility of differentiating them in these cases.

In acute cases, in which the large cells usually predominate, the staining is often very faint throughout the nucleus and protoplasm (see Plate III., b), so that at first sight we should think something was wrong with our technique. Other forms of leucocytes in the same preparation, however, will stain normally, showing that the trouble is in the lymphocytes and not in the technique. These large lymphocytes are identical in their appearance with those found at the "germ centres" of all adenoid tissue, and probably are the mother cells of the small lymphocytes. Benda has termed them "lymphogonien." They have often been mistaken for myelocytes, from which they are to be distinguished by the absence of any neutrophile granulation. They often show evidences of degeneration (see above, p. 70). The protoplasm may be entirely unstained as in most of the cells in Plate III., b, or it may stain pale gray or pink. In other specimens, especially those of the small-cell type (Plate III., a), the lymphocytes stain well. Their nuclei are frequently indented or even divided in two (this occurs also in normal blood, but less often).

Fraenkel believes still that lymphæmia, though not always acute, is usually so, and that if a chronic case takes on acute symptoms the blood becomes more lymphæmic, while if a case starts acute and becomes chronic the lymphocytes decrease. Thus a case reported by v. der Wey' of chronic myeloid leukæmia six weeks before death began to have fever, hemorrhages, great increase in the total leucocyte count and in the anæmia. No complication was present. The

<sup>&</sup>lt;sup>1</sup> Deut. Arch. f. klin. Med., vol. lvii.

lymphocytes increased 30 per cent, and the polymorphonuclear neutrophiles dropped from 30 to 3 per cent.

Gerhardt 'watched a case which began acutely with a large percentage of *large* lymphocytes and then became chronic with a predominance of *small* lymphocytes.

In acute cases Litten² has noticed fatty degeneration in the leucocytes.

The following figures illustrate the influence of a septicæmia (from suppurating cervical glands) which ended the life of No. 3 in the above Table IX.

	Date.	Number of leucocytes.	Percentage of lymphocytes.
April	3d	31,600	96.5
66	4th6th	31,000 28,505	93.6
66 66	8th	44,000 31,500	95.5
	10th	40,000	90.0
"	13th	Sepsis began. 5.661	
46	20th	4,000	
66	22d24th	$3,400 \\ 3,222$	92.
46	28th	800	0.4.19
	29theath on the 29th.	471	94.7

Zeissl's case, also of the lymphatic form, showed the following:

Date.	White cells.	Percentage of lymphocytes.	Percentage of polynuclear cells.
September 9th	80,000	96.	4.
" 24th	113,000		
" 26th	119,000		
" 29th	122,000	97.8	2.
October 6th	140,000		
	Pneumonia began.	99.	1.
" 10th	119,000		
" 11th	98,000		
" 12th	68,500		
" 13th	43,500	88.7	11.3
" 14th	50,000		
" 15th,	9,350	85.4	14.6
" 16th (A.M.)	133,200		
" 16th (P.M.)	172,000	75.	25.

Polymorphonuclear neutrophiles are absolutely as well as rela-

<sup>&</sup>lt;sup>1</sup>15th Cong. f. innere Med., 1897.

<sup>&</sup>lt;sup>2</sup>11th Cong. f. innere Med., 1893.

tively diminished in most cases. Indeed they are often so scarce that one has to look through several thousand leucocytes before finding one. There is nothing abnormal about them—a point of marked contrast with the neutrophiles in myeloid leukæmia. *Eosinophiles* and *myelocytes* are equally rare.

# Summary.

The leading characteristics of leukæmic blood are as follows:

- (a) Myeloid leukæmia.
- 1. Red cells about 3,000,000, nucleated forms very numerous.
- 2. White cells about 450,000, of which
- 3. Myelocytes form about thirty per cent.
- 4. Every possible form of cell *intermediate* between the ordinary varieties is to be seen. ("Polymorphous blood.")
  - (b) Chronic lymphatic leukæmia.
  - 1. Red cells about 3,000,000 or lower; nucleated forms rare.
  - 2. White cells about 300,000, of which
  - 3. Small lymphocytes usually form over ninety per cent.
  - 4. Myelocytes and eosinophiles very scanty.
  - (c) Acute lymphatic leukæmia.
  - 1. Red cells much diminished; nucleated forms infrequent.
- 2. Large forms of lymphocytes usually predominate; many of them often show signs of degeneration.
  - 3. Neutrophiles and eosinophiles very scanty.

# Diagnostic Value.

Leukæmia is distinguished by the blood examination from

- 1. Hodgkin's disease: (a) splenie, (b) glandular.
- 2. Tumors of the spleen and vicinity (e.g., kidney or retroperitoneal glands).
- 3. Enlargements of the lymphatic glands from tuberculosis, syphilis, malignant disease.
  - 4. Hydronephrosis.
  - 5. Huge leucocytosis from any cause.
  - 6. Chronic malaria.
  - 7. Amyloid disease.
- 1. Leukæmia and Hodgkin's disease (lymphadenoma or pseudoleukæmia). The pathology of the two diseases is identical but for the blood count. In Hodgkin's disease the blood is normal, or

shows only a moderate anemia or leucocytosis (polymorphonuclear cells alone increased), and the diagnosis is easily made.

- 2. Tumors of the spleen and especially of the kidney are very apt to be mistaken for leukæmia. Within a single year I was asked to examine the blood in three cases of "leukæmia," all of which turned out to be malignant disease of the kidney. In all of these there was a large tumor resembling the spleen in the left hypochondrium, also a very large increase of white cells. In two of them the blood was examined fresh and the great number of white cells in the slide taken as evidence confirmatory of leukæmia. The stained specimen, however, showed only marked leucocytosis with ninety per cent of polynuclear cells of the ordinary type and no myelocytes. Other large tumors of this region showed similar results. Occasionally cases of leukæmia with numerous metastases are described as "sarcomatosis," and then it is asserted that the blood of leukæmia is identical with that of sarcoma. The source of the mistake is obvious.
- 3. Adenitis with hyperplasia due to tuberculosis shows usually normal blood <sup>1</sup> and is thus easily distinguished from leukæmia. Leucocytosis is often present in syphilitic cases and still more marked in those due to cancer or sarcoma, but the counts rarely reach 30,000 and myelocytes are absent or very scanty.
- 4. One case of hydronephrosis, in which the distention of the sac was so great that it presented as a hard, solid tumor on the right hypochondrium, was taken for leukæmia by a competent observer some years ago. The normal blood examination revealed the mistake, and excluded also malignant disease in all probability. The diagnosis was reached, however, only at the autopsy.
- 5. Huge leucocytosis in pneumonia or malignant disease may cross the old boundary line of 100,000 white cells, beyond which none but leukæmic cases were supposed to venture. The differential count sets us right instantly, showing ninety per cent or so of the increase to be made up of ordinary polymorphonuclear leucocytes.
- 6 and 7. The large spleen and cachectic appearance associated with chronic malaria and long-standing suppurations may be easily distinguished from leukæmia by the absence of anything more than anæmia and leucocytosis in the blood.

<sup>&</sup>lt;sup>1</sup> Sometimes marked leucopenia.

Leucocytosis in general. Chronic malaria Amyloid disease	3,000,000 About 3,000,000 About normal Usually diminished.  Much diminished. Usually	May be over 100,000 Somewhat increased. Usually	decreased. Usually increased. Usually	Polynuclear leucocytes.  About 50 per cent. About 3 per cent. Normal.  Greatly increased. Usually decreased. Usually increased.	About 37 per cent. Absent.  Absent.  Few if any. Few if any. Few if any. Absent.	Nucleated red cells.  Very numerous. Rare.  Absent.  Few.  Few at times.  Few.  May be a few.
	Usually diminished.		Usually decreased.	Usually increased.	Absent.	May be a few.
Hydronephrosis	Normal.	Normal.	Normal or decreased.	Normal.	Absent.	Absent.

### Effect of Intercurrent Infections.

There are on record about thirty cases in which leukæmia (acute or chronic) has been complicated with some intercurrent infection, with marked effect upon the blood in all but one. This single case was an acute rheumatic arthritis reported by Richter in the discussion of Fraenkel's article in the *Deutsche medicinische Wochenschrift* for 1895 (Nos. 39, 43, and 45), p. 639. Here the blood remained unchanged.

Müller's' case of lymphatic leukæmia was complicated by a septicæmia, and the count of white cells *rose* from 180,000 to 400,000 per cubic millimetre, with a marked increase in the percentage of polymorphonuclear cells. Here was a genuine leucocytosis added to a leukæmia.

With the exception of these two cases, all those hitherto published have shown a marked progressive *decrease* in the total number of leucocytes without any change in the percentages of the different varieties in twelve, while eight showed, like Müller's, an increased percentage of the polymorphonuclear cells despite the decrease in the total leucocyte count.

Marischler<sup>2</sup> in a case of lymphatic leukæmia with cancer of the kidneys found:

	1. At First.	2. Later.
Red cells	3,450,000	2,400,000
White cells	96,000	48,000
Hæmoglobin		30 per cent

<sup>&</sup>lt;sup>1</sup> Müller: Deut. Archiv für klin. Med., 1892, vol. 1., p. 47.

<sup>&</sup>lt;sup>2</sup> Wien. klin. Woch., July 23d, 1896.

		t First.		Later.
Polymorphonuclear cells	15.6	per cent.	57.5	per cent.
Small lymphocytes	83.3	66	40.	66
Large lymphocytes		46	1.6	44
Eosinophiles		46	.16	66
Myelocytes			.16	44

Various infections—miliary tuberculosis, pneumonia, grippe, erysipelas, abscess of kidney, septic lymph glands—alike decreased the leucocyte count. In one case a rise just before death was observed.

Thus in Henck's case the leucocytes fell from 400,500 to 89,000, in one of Müller's from 246,900 to 57,300, in Kovács' from 67,000 to 17,000, in Zeissl's from 140,000 to 9,350. I have already mentioned a case of lymphatic leukæmia (page 174) in which the leucocytes fell from 40,000 to under 500, this last being on the day of death. In this case the percentages of the different varieties of leucocytes remained entirely unchanged.

Herrick ' reports a case complicated by acute streptococcus infection in which the white cells were 60,000 at the time of death. How high they may have been earlier is not known.

It appears, therefore, that when an infection complicates leukæmia we may have—

- 1. No effect (see case of rheumatic fever as a complication, just mentioned).
- 2. A genuine leucocytosis on top, so to speak, of the leukæmia, with an increased percentage of polymorphonuclear cells.
- 3. A decrease in the leucocyte count with or without an increase of polymorphonuclear cells. This decrease is by far the most common result and may go far below normal as death approaches.

Goldschneider<sup>2</sup> found that by the injection of splenic extract and other substances he could bring about a similar diminution in the number of leucocytes, but that, as in the case of intercurrent infections, this diminution was not accompanied by any improvement in the patient's condition and death followed as usual.

Abscesses occurring in leukæmic patients are filled with polynuclear leucocytes as ordinary abscesses are, and do not contain myelocytes.

<sup>&</sup>lt;sup>1</sup> Loc. cit.

<sup>&</sup>lt;sup>2</sup> Discussion of Fraenkel's article.

#### HODGKIN'S DISEASE.

(Pseudo-Leukæmia, Lymphoma).

The diagnosis of this disease is impossible without the blood count. Its pathology is identical with that of leukæmia, and even post mortem the two diseases are indistinguishable so far as the lesions outside of the blood are concerned. Yet the blood is in no way peculiar, but presents in most cases all the characteristics of the normal tissue. Its value is as negative evidence, telling us in a given case that leukæmia is absent, even though all the other signs and symptoms may be those of leukæmia.

(I.) Transitions from Hodgkin's disease to leukæmia are said to have taken place under the eyes of competent observers, but they are very rare. Only three such cases are on record so far as I know, that of Fleischer and Penzoldt, that of Mosler, and one reported by Senator, in which two sisters came under observation, both suffering from Hodgkin's disease. One died of it; in the other the blood changed to that of leukæmia before death.

Doubtless many of the other cases supposed to exemplify a similar transition were really cases in which a leucocytosis arose owing to some inflammatory complication, as not uncommonly occurs (see below, Table X.).

From the existence of these very rare cases of a transition to leukæmia, it has been supposed, especially by French observers, that Hodgkin's disease is simply an early stage of true leukæmia, and that this would always become apparent were it not that the patients die of some intercurrent disease before the signs of leukæmia have time to show themselves in the blood. One difficulty with this view is that there occur chronic cases which last from eight to ten years without any change in the blood. Another difficulty is that the transition is in fact rare, despite the relative frequency with which the disease is met with.

- (II.) Probably most cases diagnosed as Hodgkin's disease are
- <sup>1</sup> Deut. Arch. f. klin. Med., vol. xvii.
- <sup>2</sup> Ziemssen's "Handbuch d. Path. and Therap.," vol. viii.
- <sup>3</sup> Berl. klin. Woch., 1882, p. 533.
- <sup>4</sup> It is noteworthy that all these cases are of some years' standing—before Ehrlich's methods were much used. Askanazy has more recently observed the transition in a case in which the blood was normal for two and a half years and then leukæmic for one and a half years under observation (quoted by Pinkus in Nothnagel's "Specielle Path. and Therap.," vol. viii.).

in fact cases of glandular hypertrophy due to syphilis or tuberculosis, and this fact has led many to the belief that *all* cases called Hodg-kin's disease are in reality only syphilitic or tuberculous adenitis.

In a considerable number of cases, however, tuberculosis has been disproven by careful inoculation experiments with the glandular tissue, and there is no reasonable doubt that *some* cases at any rate are not due to tuberculosis or syphilis. Probably the diagnosis can never be made with absolute certainty during life.

- (III.) The frequent occurrence of fever and other symptoms characteristic of an infectious disease has led some writers to class it as such. In a certain percentage of cases the disease (like leukæmia) has run an acute course, lasting not more than six weeks from the first symptoms to death. In some chronic cases the same sort of evidence of an infectious nature has been brought forward. Ulcerations occur in the mouth and intestine, through which morbid products might gain admission. Various bacteria (pyogenic and others) have been found in the blood and tissues from time to time, but numerous negative examinations for micro-organisms are also on record, and the evidence is insufficient to establish the infectious nature of the disease. None the less, there is a growing tendency among the leading writers and observers in Germany and elsewhere, to believe that the disease will ultimately be shown to be tuberculous.
- (IV.) Meantime most surgeons continue to regard it as a form of sarcoma¹ and to treat it like malignant disease.

#### The Blood.

Whatever the nature of the disease, we find in the earlier stages of most cases normal blood, as will be seen in Table X. (cases 7 to 23 inclusive).

As the disease progresses the hæmoglobin soon begins to fall, later the red cells do so, until, as at the end of Case 10 of the present series, the blood may reach the severest grade of anæmia. In acute cases the anæmia may develop very rapidly. The usual qualitative changes characterizing severe secondary anæmia may be present.

#### White Cells.

When inflammation arises in the glandular tumors and sometimes when none is found, the white cells may be greatly increased, even up to a ratio of 1:80 red cells, as in Case 1 of the present

 $^{\rm 1}{\rm There}$  are no reliable differentia between sarcoma of lymph glands and "benign" lymphoma histologically.

TABLE X.—HODGKIN'S DISEASE.

				LADIA		ODURIA S DISEASE.
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	28	F.	5,500,000	64,000	75	Polymorphonuclear cells, 95 per cent. Lymphocytes, 5 per cent.
2	* * * * * * * *	М.	3,848,000	39,200	48	Acute. Diff.* 500. Polymorphonuclear cells, 95.2 per cent. Lymphocytes, 4.6 per cent.
3	24	F.	4,886,000	32,000	53	
4	19	F.	5,528,000 5,160,000	22,200 25,400		Diff. 200 cells. Polymorphonuclear cells, 86.5 per cent. Six weeks later. Lymphocytes, 12.0 per cent. Eosinophiles, 1.5
5	19	M.	2,480,000	20,200	33	Stained specimens normal.
6	26		5,148,000	14,000 21,200	60 50	June 6th. June 11th. Polynuclear, 92.8 per cent. Small lymphocytes, 3.6 per cent. Large lymphocytes, 3.0 " Eosinophiles, 2 " Myelocytes, 2 " No nucleated reds. Reds pale. Some few irregular in shape.
7	28		4,312,000	12,000	42	Polynuclear, 90.5 per cent. Lymphocytes, 7.5 "Eosinophiles, 2.0 "
-8	59			8,500	68	
9	28		3,760,000	7,000	65	
10	34		3,380,000 3,512,000 2,960,000 2,828,000	6,800 6,700 6,300 7,900 7,600	40 40 32 28	Polynuclear, 84.6 per cent. Small lymphocytes, 10.0 " Large lymphocytes, 3.2 " Eosinophiles, 1.4 " Myelocytes, .8 " Normoblasts = 1 November 29th. December 5th. December 5th. December 9th. December 27th. December 27th.
11	27			6,200 7,200		February 19th. Count 300. Polynuclear, 89.0 per cent. Large lymphocytes, 2.0 " Small lymphocytes, 8.7 " Eosinophiles, 3 "
12	43		2,880,000	5,000 3,800 5,200	30 30 30	January 6th. Count 500. Polynuclear, 57.6 per cent. Small lymphocytes, 29.9 " Large lymphocytes, 12.5 " Eosinophiles, 7 " Mast cells," ,3 " Reds rather pale. Iar in shape.  January 13th. January 15th. January 31st. Polynuclear, 63.2 per cent. Small lymphocytes, 34.0 " Large lymphocytes, 2.8 " Eosinophiles, 0.0 " Megaloblasts = 1.0 Normoblasts = 0.0 Reds as before.

<sup>\*</sup> Diff. = Differential count of.

Table X.—Hodgkin's Disease (Continued).

-						
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
				3,000	30	February 8th. Polynuclear, 55.4 per cent. Large lymphocytes, 8.6 Small lymphocytes, 36. Eosinophiles, 0. "
			3,252,000	3,400	30	Reds as January 31st. February 13th. Polynuclear, Smail lymphocytes, 32.2 Large lymphocytes, 6.4
			2,012,000	5,000	28	February 23d. Polynuclear, 70 per cent. Small lymphocytes, 26 " Large lymphocytes, 4 " Eosinophiles, 0 "
13	44		2,336,000	3,400	30	May 4th. Count 500 cells, Polynuclear, 82.0 per cent. Small lymphocytes, 15.6 " Large lymphocytes, 2.4 " Eosinophiles, 0.0 " No nucleated reds. Reds stain rather palely. Little variation in size.
			2,140,000	4,000	35	May 28th. Polynuclear, 70 per cent. Small lymphocytes, 18 Large lymphocytes, 12 Eosinophiles, 0 " Reds similar to May 4th.
14	28					Polynuclear, 69 per cent. Lymphocytes, 26 "Eosinophites, 5"
15	37	M.	5,990,000	13,500		Polymorphonuclear cells, 95 per cent. Lymphocytes, 5
16	25	M.	5,440,000	9,500	59	Death; autopsy.
17	19	F.	5,724,000	6,800	42	Polymorphonuclear cells, 50 per cent. Lymphocytes, 40 "."
18	Adult.	М.	3,652,000	5,800		Diff. 300. Polymorphonuclear cells, 50.0 per cent. Lymphocytes, 45.3 ". Eosinophiles, 1.3 ". Myelocytes, 1.7 ". Big spleen, pallor, nosebleed, debility.
19	29	M.	5,210,000 3,840,000 1,000,000	5,000 4 5,600		Two months later. Three weeks "
20	58	М.	2,820,000	4,800	60	Polymorphonuclear cells, 80 per cent. Lymphocytes, 17 '' Eosinophiles, 3 ''
21	21	М.	4,560,000	4,000 5,800		
22	23	М.,	4,210,000	3,332		Myelocytes, 1 per cent. Big liver and spleen. Eosinophiles, 4
23		М.	3,800,000	1,440	67	Diff. 500. Polymorphonuclear cells, 71.25 per cent. Lymphocytes, 28.00 "Eosinophiles, .75 "One normoblast."
24				No leucocy- tosis.		Diff. 200. Polymorphonuclear cells, 63.5 per cent. Lymphocytes, 36.5 Eosinophiles, 1.0 "  Many of the lymphocytes have two nuclei.

TABLE	X.—Hodgki	n's Diseas	E (Continued).
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No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
25				No leucocy- tosis.		Diff. 300. Polymorphonuclear cells, 41.7 per cent. Lymphocytes, 48.4 cosinophiles, 9.3 Myelocytes, .6 "
26	4	M.		No leucocy- tosis.		Diff. 500. Polymorphonuclear cells, 60.2 per cent. Lymphocytes, 36.0 "Eosinophiles, 3.6 "Myelocytes, .2 "Two normoblasts.
27		F.		•••••		Diff. 500. Polymorphonuclear cells, 92.6 per cent. Lymphocytes, 5.2 "Myelocytes, 2.2 "No eosinophiles.
28				No leucocy- tosis.	• • • • • • • • • • • • • • • • • • • •	Diff. 313. Polymorphonuclear cells, 62.3 per cent. Lymphocytes, 37.0 "Myelocytes, .6 "
29	28	М.	5,218,000	11,800	85	Polynuclear, 51 per cent. Small lymphocytes, 35 Large 7 Eosinophiles, 7
30	30	M.	5,280,000	6,800	55	Diff. Polymorphonuclear cells, 76.0 per cent. Lymphocytes, 22.3 " Eosinophiles, 1.4 " Myelocytes, 3 " No nucleated red cells.
31	32	M.	4,616,000	2,400	70	
32				2,200	••••	Diff. Polymorphonuclear cells, 69 per cent. Small lymphocytes, 19 Large 18 Eosinophiles, 4 Few normoblasts.

series. There is, however, no more resemblance to leukæmia than in any other form of leucocytosis, the polymorphonuclear cells alone being increased. There is no reason for supposing, as Reinert' does, that relative diminution of the lymphocytes is owing to the diseased condition of the lymph glands, nor for believing with Pinkus (Nothnagel's "Specielle Path. and Ther.," vol. viii., 1901) that the relative increase of lymphocytes which some cases show is characteristic of Hodgkin's disease. Pfeiffer' has recently reported a case of the cutaneous form of the disease with sixty per cent of lymphocytes out of a total leucocyte count of 6,500.

As in any other cachectic condition, small numbers of myelocytes may be found. They were seen in nine of our cases out of twenty-five in which a color analysis was made, the highest percent-

<sup>&</sup>lt;sup>1</sup> "Die Zählung der Blutkörperchen." Berlin, 1891.

<sup>&</sup>lt;sup>2</sup> Pfeiffer: Wien. klin. Woch., 1897.

age being two per cent. Eosinophiles are usually decreased when leucocytosis is present.

### Summary.

Normal blood in early stages.

Later often marked anæmia; sometimes leucocytosis.

# Diagnostic Value.

The only help given us by the blood is in excluding leukæmia. Syphilis, tuberculosis, or malignant disease might cause similar blood changes or lack of changes.

### EFFECTS OF SPLENECTOMY ON THE BLOOD.

When splenectomy is performed for abscess, hydatid, rupture of the spleen, or other local disease, it is followed, after a varying number of weeks, by a hyperplasia of the lymph glands, associated with *lymphocytosis*. How long this lymphæmia lasts is not altogether clear.

Later, after many months, a moderate eosinophilia may appear and the mast cells are increased. Ehrlich examined one case six months after operation in which a considerable lymphæmia existed, the bulk of the lymphocytes being large. Eosinophiles were not increased. In another case he found the lymphæmia persisting in the fifth year after operation, while the eosinophiles were between three and four per cent. In two other cases he found (six and eighteen months after the operation) no lymphocytosis.

In the following table the records of four other cases are given:

Large lymphocytes. Small lymphocytes. Polymorpho-nuclear neutrophiles. Rosinophiles. White Red cells. Remarks. Case. 63 4,570,000 8.000 Before operation. 64 Three days after. 4.970,000 30,000 77 5,180,000 65,000 Six days after. 17.500 11.700 4,800,000 66 Forty-eight days after. 4.353,000 85 Four months after. 3,300,000 85 11,600 Five years after. \*2 3,200,000 53,000 65 (1893, for abscess.) Three weeks after.

TABLE XI.

<sup>\*</sup> Czerny: Cited in Laudenbach: Arch. de Physiol., 1896, p. 724.

TABLE	XI.	(Continueà	().
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case.	Red cells.	White cells.	Per cent hæmoglobin.	Po'ymorpho- nuclear neutrophiles.	Small lymphocytes.	Large lymphocytes.	Eosinophiles.	Average diameter of red cells.	Remarks.
†3	4,500,000 1,634,000	13,800 12,000	80 45	61	16	20	3	8.1 μ	Four months after. Operated (April 9th, 1893) for malarial hyper- trophy with twisted pedicle. April 23d.
	2,460,000	20,000	87	49	18	32	1		May 6th.
	4,530,000	27,000	110	66	18	15	1	$7.7 \mu$	May 13th, 1894.
	3,977,000	8,000	100	62	21	11	6		October 2d, 1895.
<b>†</b> 4	4,850,000	30,000	108	83	8	8	1		Operated for hypertro- phied, wandering spleen. Before opera- tion.
	4,700,000	39,000	100	91	5	4	0		Seven days after.
	3,630,000	18,000	105	78	15	6	1		Two months after.
	2,750,000	20,000	* 63	84	5	10	1		Three years after.

<sup>+</sup> Hartman and Vaquez: Soc. de Biol., February 5th, 1895.

One point which these cases clearly prove is that no one variety of leucocyte is supplied to the blood from the spleen.

#### SPLENIC ANÆMIA.

(Pseudo-Leukæmia Splenica, Anæmia with Enlarged Spleen.)

I object to the term "splenic anæmia," because it seems to suggest that the splenic enlargement is in some way the cause of the anæmia, and for this there is no sufficient evidence. But, whatever term is used, there is at least one point about the blood of cases of idiopathic anæmia occurring in adults and associated with enlarged spleen which deserves notice. This is the leucopenia. In Osler's article (Am. Jour. Med. Sciences, January, 1900) the following counts are recorded:

Case.	Date.	Red cells.	White cells.	Hæmo- globin, per cent.	Poly- nuclears, per cent.	Lympho- eytes, per cent.	Eosino- philes, per cent.	Remarks.					
I.	Feb. 1879.	2,250,000	7,100	••		••		Recurring hæmatemesis and melæna. Death in an attack of melæna in 1897.					
II.	1898.	3,000,000	2,800	25	84.4	12.8	2.8	Hæmatemesis for years at intervals. Splenectomy. Recovery,					

Case.	Date.	Red cells.	White cells.	Hæmo- globin, per cent.	Poly- nuclears, per cent.	Lympho- cytes, per cent.	Eosino- philes, per cent.	Remarks.
III.	1898.	4,000,000	6,500	30	73	25	2	Hæmatemesis and melæna frequently.
IV.	1895.	4,816,000	5,000	55				
v.	1896.	3,600,000	3,000	66	66	31	1	
VI.	1897.	4,788,000	5,200	60	40	59	1	
VII.	1898.	4,128,000	2,800	45				
VIII.	1898. Jan. June.	3,328,000 2,500,000		40 45	78	21.5	.5	Occasional normoblast.
IX.	1899.	4,208,000	4,000	45	65	31.2	3.3	
X.	1899. Oct. 12th.	1,540,000	3,300	23	74	23.8	1.5	Myelocytes, 1.5 per cent. While counting 300 leucocytes, saw  § Normoblasts, 32.
	" 17th.	1,380,000	3,250	20		•		) Megaloblasts, 13. While counting 400 white cells, 75 nucleated reds were seen, 21 of which were normoblasts, 19 megaloblasts, and 35 intermediate.
	Nov. 10th. 20th.	3,120,000 3,680,000		55 54				No nucleated reds.
XI.	1899. Oct. 31st. Nov. 16th.	3,856,000 3,992,000		55 60	73.7	25.3	1	
XII.	Nov. 18th. 1899.	4,270,000	2,500	45	80.3	14	5	Mast cells, 6 per cent.

In eight of these twelve cases the leucocytes were markedly subnormal. In my own series (see following table) this abnormality is still more evident.

### SPLENIC ANÆMIA.

	Age.	Sex.	Red cells.	White cells.	Hæmoglobin, per cent.	Remarks.
1	24	••	2,668,000	15,800	35	Polynuclear, 62. per cent. Lymphocytes, 36. "Eosinophiles, .4 "Myelocytes, 1.2 "Basophiles, 4.
2	12	• •	2,268,000	9,800	25	With neck glands. Polynuclear, 74. per cent. Lymphocytes, 25. " Myelocytes, 1. " Normoblasts, = 4. (Count 500.)
			3,320,000 3,336,000		22 25	20 days later. 56 " "

# HOKGKIN'S DISEASE.

# SPLENIC ANÆMIA.—Continued.

	Age.	sex.	Red cells.	White cells.	Hæmoglobin, per cent.	Remarks.
3	13		4,280,000	2,100	42	Polynuclear, 59. per cent. Lymphocytes, 40. " Eosinophiles, 1. " No nucleated reds.
			2,224,000	1,300 6,400	48 30	7 days later. 15 " " dying of hemor- rhage.
4	18	• •	384,000	1,800	35	Polynuclear, 55. per cent. Lymphocytes, 37.5 " Eosinophiles, 7.5 " No nucleated reds.
				1,900	45	8th day.
			4,024,000	1,450	35	12th day.
5	4 ==		9.040.000	1,500	0.5	15th day.
9	45	••	3,048,000	1,600	35	Polynuclear, 44. per cent. Lymphocytes, 55. " Eosinophiles, 1. " Two normoblasts. (Count 500 cells.)
6	17		2,560,000	700	20	July 21st.
				650		Repeated. Polynuclear, 66%. Lymphocytes, 33. per cent. Eosinophiles, 1. " (No nucleated in 150.)
				1,700		July 27th.
			0.450.000	900	12	July 31st.
			2,456,000	2,200	$\frac{45}{40}$	August 11th.
			4,912,000	1,400	50	August 20th. November 18th. Following
			1,012,000	1,400	00	July 5th, doing well.

# PART II.

# ACUTE INFECTIOUS DISEASES.

### CHAPTER III.

# INFLUENCE OF FEVER ON THE BLOOD.

Some of the blood changes found in acute infections are to be regarded as due simply to the fever associated with the disease. It is worth while, therefore, to consider what fever *per se* can do to the blood.

Maragliano' and others have shown that during fever from any cause a *contraction* of the peripheral vessels occurs. When fever disappears, whether spontaneously or from the action of antipyretics (phenacetin, quinine, etc.), a *dilatation* of the vessels follows.

Following the laws to which we have so often alluded, the contraction of the vessels causes a concentration of the blood with rise in specific gravity and in the number of blood cells per cubic millimetre. This concentration is still further increased by the greater loss of water which the organism suffers during fever than under normal conditions.

The effect of these two influences in increasing the number of red cells per cubic millimetre is, however, counteracted to a considerable extent by the sharing of the blood in the general tissue destruction which goes on with increased rapidity during fever. Many corpuscles are thus destroyed, but until the temperature falls the anæmia is covered up by the concentration. When the fever leaves the patient there is a sharp fall in the number of cells per cubic millimetre, due partly to the destruction of corpuscles (hitherto masked by concentration) and partly to the dilution of the blood which is the result of the post-febrile dilatation of the peripheral vessels above mentioned. The suddenness of this fall in the count is proportional to the suddenness of the fall in temperature.

The alkalinity of the blood has been often said to be diminished

<sup>1</sup> Zeit, f. klin, Med., vols, xiv, and xvii.

in fever, but recent research tends to show that these results were obtained by faulty technique, and it is doubtful whether the reaction of the blood shows any constant changes in fever.

Leucocytes and fibrin show no constant changes, though in the majority of infectious fevers they are increased.

#### PNEUMONIA.

#### The Blood as a Whole.

(a) Bacteriology.—The diplococcus lanceolatus has been found in the blood of pneumonic patients repeatedly, especially in those in whom there has been some secondary diplococcus infection (e.g., diplococcus endocarditis); but such findings are rare and have generally been in fatal cases with very severe generalized infection.

For example, Sittmann¹ out of 16 cases found diplococci in the blood of 6, most of which were complicated with lesions in other organs, and 4 of which were fatal, while of the 10 whose blood was sterile, 9 ended in recovery.

Boulay<sup>2</sup> found the organism in 2 cases shortly before death. Belfanti 3 found it but 6 times out of a large number of cases, and of these 6, 5 were fatal. Goldschneider and Grawitz got similar results. Cohn<sup>6</sup> in 32 cases found the organism in 9; 7 of these The other 2 had empyema and other evidences of were fatal. metastatic action of the pneumococci. Beco<sup>7</sup> studied 49 cases. Twenty of these ended fatally, and of these 20 there were 5 whose blood showed pneumococci by culture and 1 from which Friedländer's bacillus was cultivated. Out of 29 cases ending in recovery only 2 showed cocci in cultures from the blood. If large numbers of colonies can be cultivated from the peripheral blood, Beco considers the prognosis grave. A few colonies, however, are of no significance in prognosis. Fraenkel has obtained over 300 colonies from one puncture. Their virulence was less than that of those in the sputa, showing apparently the effects of the blood's antitoxic power. Nevertheless, it is obvious that the presence of pneumococci in the blood is a bad prognostic sign.

<sup>&</sup>lt;sup>1</sup> Deut. Archiv f. klin. Med., 1894, p. 323.

<sup>&</sup>lt;sup>2</sup> Paris Thesis, 1891.

<sup>&</sup>lt;sup>3</sup> Riforma Medica, Naples, 1890, No. 37.

<sup>&</sup>lt;sup>4</sup> Deut. med. Woch., 1892, No. 14.

 <sup>&</sup>lt;sup>5</sup> Grawitz: Charité-Annalen, vol. xix.
 <sup>6</sup> Cohn: Deut. med. Woch., 1897, No. 9.

<sup>&</sup>lt;sup>7</sup>Beco: Revue de Méd., 1899, July 10th.

- (b) Coagulation is remarkably rapid, and in fresh specimens the fibrin network is very thick and appears within a few minutes, except in the rare cases with subnormal leucocytes. Here it may be absent or diminished.
- (c) In cases with cyanosis the blood is often concentrated at the periphery so that its specific gravity is high and the number of corpuscles large.
- (d) Monti and Berggrün' observed that in children the specific gravity was high throughout the course of the disease, falling with the temperature.

The toxicity of the blood is doubled (Albu: Virchow's Archiv, vol. 149).

### Red Cells.

During the fever the red cells are approximately normal (unless increased by cyanosis); but after the crisis there is often slight anæmia, and sometimes a severe one. The hæmoglobin is more markedly and more lastingly reduced than the number of red cells.

A more interesting and important observation was made by Türck in 1898, viz., that when the infection is severe or the patient of low vitality nucleated red cells (mostly normoblasts) may appear in the peripheral blood. In all Türck's cases megaloblasts as well as normoblasts occurred, but the latter were greatly in the majority. Dr. Badger and I studied a most interesting case of this type in 1898. The pneumonia ran a severe course and was followed by an empyema which proved fatal. The blood counts were made for the most part after the crisis. At autopsy the marrow of the femur was bright red from end to end. The blood showed the following:

Date.	Red cells.	White cells.	Haemo- globin, per cent.	Poly- nuclears, per cent.	Lympho- eytes, per cent.	Kosmo- philes, per cent.	Myelo- cytes, per cent.	Number of white cells counted.	Normo- blasts.	Megalo- blasts.
1898—										
January 13th		61,000	45							
" 14th		71.500		90.0	7.0		3.0	600	20	15
" 15th	4,520,000	59,000		84.5	8.0		7.5	600	93	15
" 16th		51,800		84.5	12.8	0.2	2.5	600	54	4
17th		47.000		86.6	6.1	0.8	6.5	700	24	3
18th		26,700		87.2	10.0		2.5	500	?	?
19111		19,700						****	1.1	
AULII		25,000		92.5	7.5			400	3	-:
2181		24,000		92.0	7.6	0.00	0.3	300	3	1
and		14.400		87.0	12.5	0.25	0.25	400		
24111		14,400							***	
" 26th		19,100								

Many of Türck's stimulation forms and many neutrophiles intermediate between myelocytes and polynuclear cells were seen.

<sup>&</sup>lt;sup>1</sup> Arch. f. Kinderheilk., vol. xvii.

Maragliano has noticed "degenerative" changes in the red cells in severe cases.

# White Corpuscles.

- 1. Probably as early as the time of the chill, and certainly within a few hours after it, the leucocytes are greatly increased, and usually continue so throughout the febrile period.
- 2. There is no correspondence between the daily variations in temperature and the leucocyte curve. In cases in which a pseudocrisis occurs (the temperature falling but rising again), the leucocyte count usually remains high, while at the time of the true crisis and often a few hours before it the leucocytes begin to fall. This fall, however, is hardly ever by "crisis," but though starting perhaps a little before the temperature it is one to two days longer in reaching normal. When the temperature reaches normal by lysis the leucocytes fall with it, but generally more slowly, and reach normal later.
- 3. When resolution is delayed the leucocytosis continues, sometimes for weeks, and very gradually falls to normal in cases in which resolution eventually occurs without complication. If abscess, empyema, or gangrene follow, the leucocytes usually become still further increased.
- 4. The degree of leucocytosis is probably the resultant of the factors mentioned on page 105, and does not run parallel to the degree of fever or the amount of lung involved. Nevertheless, cases with extensive signs in both lungs, and especially those complicated by empyema or other suppuration, are more apt to have very high counts, provided the "reaction" of the patient against the infection is vigorous. Children have especially high count as a rule (see exception below). The cases appear to fall into the following groups as regards the degree of leucocytosis present.
  - 1. Mild infection, vigorous reaction = slight leucocytosis.
  - 2. Severe or moderate infection, vigorous reaction = marked leucocytosis.
  - 3. Severe infection, feeble reaction = no leucocytosis.
- (a) The patients in Class 1 all recover, but they are very few in number. (b) Those in Class 2, which includes over nine-tenths of all cases, may or may not recover, according as the fight between patient and disease comes out one way or the other.
- (c) Those in Class 3 almost invariably die; there is not sufficient of a struggle to raise the leucocyte count. A striking exception to

this rule is reported by Stockton (*Phil. Med. Jour.*, June 25th, 1898), a case of lobar pneumonia in a child of eight with three relapses and a total course of sixty-eight days. At the height of the second relapse the blood was examined and showed only 4,000 leucocytes per cubic millimetre. Of these there were forty-four per cent of polymorphonuclear, fifty per cent small lymphocytes, six per cent large lymphocytes. In the second apyretic interval, sixteen days after the first examination, the count stood 7,840 leucocytes per cubic millimetre. Of these thirty-four per cent were polymorphonuclear, sixty per cent small lymphocytes, and twenty per cent eosinophiles, four per cent large lymphocytes (?).

After the third seizure (three weeks later) the leucocytes were 10,080, with polymorphonuclear forty-five per cent. Small lymphocytes forty-six per cent, eosinophiles eight per cent, large lymphocytes one per cent.

On the sixty-eighth day (in convalescence) the blood showed: Red cells, 4,952,000; white cells, 7,600; hæmoglobin, 90 per cent. Polymorphonuclear, 57; small lymphocytes, 36; large lymphocytes, 2.5; eosinophiles, 4.5.

Very possibly this infection may have been due to some other organism than the diplococcus lanceolatus.

When either the patient or his disease easily gains the mastery there is no leucocytosis, or a very slight one; but in the much larger class of cases in which the struggle is a fierce one, leucocytosis appears, whichever way the struggle results.

Pick 'noted that pneumonia complicating smallpox when the patients were already very sick, caused no leucocytosis, and the same is often true in those whose power of resistance is reduced by age, alcoholism, typhoid, or by some chronic disease.

Von Jaksch, noticing the fatality of cases without leucocytosis, suggested that we should induce leucocytosis by injecting turpentine or other irritants so as to cause abscess; but this has not proved of any benefit to the patient, nor has the production of leucocytosis without abscess, as can be done with pilocarpine or nuclein, been any more successful. There is no difficulty in producing the leucocytosis by these means, but all observers are agreed that it does the patients no good.

Leucocytosis is checked by antipyretics (Hare<sup>2</sup>) but not by cold

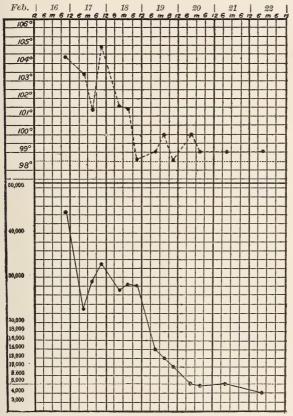
<sup>&</sup>lt;sup>1</sup> Arch. f. Dermat. und Syph., vol. xxv., p. 63.

<sup>&</sup>lt;sup>2</sup> New York Medical Record, May 9th, 1896.

bathing, which speaks in favor of the latter method of reducing temperature.

The general course of the leucocytes is seen in the accompanying charts from Billings, to whose excellent article I am greatly indebted.

CHART I.—PNEUMOMIA, SHOWING FALL BY CRISIS (BILLINGS).

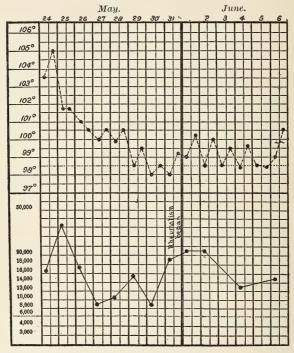


The upper chart shows the course of the temperature, the lower that of the leucocytes.

Qualitative Changes.—As in most forms of leucocytosis, the polymorphonuclear leucocytes are enormously increased both absolutely and relatively, often making over ninety per cent of all the white cells. Eosinophiles and blood plates disappear and the lymphocytes are absolutely and relatively much reduced. After the crisis

this is reversed, the polymorphonuclear forms falling often below sixty per cent, while the eosinophiles and blood plates are above normal. The return of the eosinophiles to the circulation often occurs a day or two before the crisis. It seems to mean that the acme of the process has passed, and so constitutes a favorable sign in

CHART II.—PNEUMONIA AND RHEUMATISM.



The upper chart shows the course of the temperature, the lower that of the leucocytes.

most cases. After the crisis the eosinophiles may run up to five to six per cent (300-450 absolute).

Myelocytes may be abundant (11.9 per cent or 1,056 absolute) and stimulation forms and transitional neutrophiles numerous. They have no known prognostic significance.

At and just after the crisis a great increase of blood plates takes place, gradually disappearing later.

As to the differential count in the (fatal) cases in which leucocytosis is absent, data are scanty. Bieganski thought the polymor-

phonuclear varieties decreased, Rieder found them increased, while Billings finds them normal. No general law can be stated on this point as yet.

In a case of bronchopneumonia complicating pertussis studied at the Mass. General Hospital in 1894, the conditions were entirely different from those just stated. The patient, a girl of six, had at entrance 72,100 leucocytes per cubic millimetre. Two days after the count was 94,600. A differential count made at the same time showed that the small lymphocytes made up 66 per cent of all the 94,600 leucocytes per cubic millimetre. The polymorphonuclear cells were reduced to 30 per cent. Lymphatic leukæmia was thought of, but the leucocytosis was gone in ten days, and within a fortnight the patient left the hospital well. In the light of recent studies in pertussis this is now explicable (see below, p. 218).

# Diagnostic and Prognostic Value.

1. In cases of so-called "central pneumonia" in which the symptoms but not the physical signs of the disease are manifest, the presence of a well-marked leucocytosis is often of great diagnostic value. It excludes malaria, typhoid, and uncomplicated grippe as causes of fever, and if scarlet fever and suppuration can be excluded by other evidence, it makes pneumonia very probable.

I have repeatedly seen the diagnosis of pneumonia made in the absence of physical signs and largely on the evidence of the blood count, the diagnosis being confirmed several days later by the appearance of typical signs of consolidation. In a patient of Dr. F. C. Shattuck's, sick five days, yet showing no signs of consolidation of the lung, the presence of a marked leucocytosis excluded typhoid, the only other likely diagnosis, and led Dr. Shattuck to treat the case as pneumonia, the wisdom of which course was later demonstrated by the appearance of signs of consolidation.

- 2. Between pneumonia and capillary bronchitis the condition of the blood is of no help, as the latter also causes leucocytosis, and some cases affecting the larger tubes do the same.
- 3. In cases of pneumonia occurring in very old or very young people, in which the fever and symptoms may be very slight, the presence of leucocytosis may be the first thing to direct our attention to the lungs, dyspnea and cough being absent.

<sup>&</sup>lt;sup>1</sup> Stiènon: Jour. de Méd., de Chirurg. et de Pharm., Bruxelles, 1895, t. iv., fasc. 1.

In prognosis, the important point is that the absence of leucocytosis is a very bad sign, while its presence is neither good nor bad. It must be remembered also that in the very mildest cases we may find the same absence of leucocytosis which in any other but the mildest would be almost surely fatal.

This last point, which appears to me of great importance, is illustrated by the following figures:

Halla reported 14 cases; 2 had no leucocytosis, and both were fatal.

Billings reported 22 cases; 1 had no leucocytosis and was fatal. Laehr with 16 cases, and Rieder with 26, got similar results.

Ewing in 101 cases found leucocytosis absent in 6; 6 were fatal. Von Jaksch and Kilodse likewise maintain that the absence of leucocytosis is usually fatal.

In the Massachusetts General Hospital 566 cases have been studied. In general they entirely confirm the results obtained by Billings and summarized above: 62 of them presented no leucocytosis at any time, and of these 50 were fatal, another one seemed moribund but finally recovered.

The evidence, therefore, is in favor of the view that when leucocytosis is persistently absent in any but the mildest cases the prognosis is almost fatal. The presence of leucocytosis, on the other hand, is no guaranty whatever of a favorable issue.

Reappearance of eosinophiles is a favorable sign in most cases.

The series of cases at the Massachusetts Hospital is too large to exhibit in tabular form. Their results may be summarized as follows:

Cases	with	leucocyte	s under 10	000 = 62		(50 of these fatal)
46	66	"	between	10,000	to	15,000 = 82
66	66	44	66	15,000	66	20,000 = 138
44	44	"	"	20,000	66	25,000 = 121
44	66	66	44	25,000	66	30,000 = 76
44	66	44	44	30,000	44	35,000 = 32
66	66	66	"	35,000	66	40,000 = 21
66	46	66	"	40,000	44	45,000 = 16
44	66	66	44	45,000	46	50,000 = 7
66	66	66	"	50,000	66	55,000 = 7
44	66	"	44	55,000	66	60,000 = 1
44	44	66	66	60,000	46	65,000 = 1
66	44	46	"	65,000	66	70,000 = 1
44	66	44	66	100,000	66	110,000 = 1

#### Broncho-Pneumonia.

In forty-nine cases of broncho-pneumonia recorded at the Massachusetts General Hospital, the following counts are recorded.

```
Between 5,000 and 10,000 = 8
         10.000 "
                     15,000 = 13
         15,000 "
                    20,000 = 22
    46
         20,000 "
                    25,000 = 22
   66
         25,000 "
                    30,000 = 4
   44
         30,000 "
                    35,000 = 5
   44
         35,000 "
                    40,000 = 1
         40,000 "
   66
                    45,000 = 2
   66
         45,000 "
                   50,000 = 2
   46
         50,000 "
                    55,000 = 1
   66
        100,000 "
                   185,000 = 3 (same case)
                             83
```

The highest counts in this series were in a case of broncho-pneumonia in a baby of fifteen months. As the lymphocytes made up the larger part of the increase, and as the cough came in paroxysms with great cyanosis, pertussis was suspected. This case has already been referred to on page 114, and a similar case is recorded on page 195.

#### TYPHOID FEVER.

# Bacteriology of the Blood.

Although it has long been known that the bacilli of Eberth could occasionally be found in the circulating blood or in the rose spots of typhoid cases, yet it is only within the last few years that such findings have been sufficiently constant to be of any practical value in diagnosis.

Kühnau using 5-10 e.e. of blood found typhoid bacilli in two out of four cases.

Neufelt (Zeit. für Hygiene, xxx., 3, p. 499) acted upon the belief that typhoid bacilli find lodgment in the skin, protected from the destructive agencies which ordinarily destroy them in the circulating blood. In the skin the bacilli produce the rose spot. In the attempt to cut out a rose spot for the purpose of cultivating the bacilli, the blood which flows from the cut must be instantly diluted, else it will kill off the now exposed bacilli on the spot.

By excising several spots, Neufelt succeeded in cultivating the

bacilli in thirteen out of fourteen cases of typhoid fever. The results often gave proof of the nature of the disease before the Widal reaction had appeared. Curschmann (Münch. med. Woch., November 28, 1899), using not over two spots in each case, but following in other respects Neufelt's technique, got positive results in fourteen cases out of twenty.

Richardson (*Phil. Med. Journal*, March 3, 1900) got positive results in five cases out of six.

# Quantitative Changes.

- 1. The blood plates are usually scanty, and the amount of fibrin is diminished. In one of Türck's cases, blood plates and fibrin were nearly absent, and a hemorrhagic diathesis developed. He considers a rapid falling off of the amount of fibrin and blood plates a bad prognostic sign, but in a case of hemorrhagic typhoid reported by Hamburger (Johns Hopkins Hospital Report, vol. viii.) recovery took place although the coagulation time was ten minutes.
  - 2. Specific gravity follows the course of the hæmoglobin.
- 3. The general effects of fever (see above, page 188) are in part accountable for the changes next to be described, while some of them are more peculiar to typhoid fever.

## Red Cells.

In Thayer's admirable study (Johns Hopkins Hospital Reports, vol. viii.) we find the following analysis of two hundred and sixty-five counts.

WEEKLY AVERAGE BASED ON ONE COUNT PER WEEK IN EACH CASE, THE
AVERAGE BEING TAKEN FOR THE WEEK IN EVERY CASE IN WHICH
MULTIPLE COUNTS WERE MADE.

1st	week	32 count	ts	4,913,312
2d	44	83 "		4,706,855
3d	44	54 "		4,555,814
$4  ext{th}$	66	34 "		4,187,720
$5 ext{th}$	66	22 "		4,118,590
$6 \mathrm{th}$	66	87 "		4,028,428
$7  ext{th}$	66	8 "		3,309,125
8th	. "	8 "		3,652,285
9th	L 66	6 "		3,509,666
10 th	66	1 count		3,920,000
11th	£ "	1 "		2,109,333

All these counts refer to the febrile period of the disease.

Eighty counts were made during convalescence. The results were as follows:

ESTIMATES OF THE RED BLOOD CORPUSCLES DURING CONVALESCENCE, ARRANGED ACCORDING TO THE PERIOD AFTER THE LAST DAY OF FEVER.

1st	week	, 32	count	s.													4,540,000
2d	66	22	44				 	,							٠.	 	4,637,100
3d	66	15	44		 		 										4,252,000
4 th	66	6	46														4,391,000
5th	66	2	66				 										5,469,000

Thayer comments: "It will be noticed that in the first week (of fever) the number of red blood corpuscles is already somewhat below the normal"—that is taking the normal as from 5,500,000 to 6,000,000, as it seems proper to do in this country (see page 56).

From this point it steadily sinks week by week for the first nine weeks. After that the number of counts is too small to justify conclusions. The lowest point is probably reached about the end of defervescence in the majority of uncomplicated cases, yet when defervescence is slow, blood regeneration may begin well before the end of the febrile period. In the first two weeks of convalescence, regeneration is going on slowly. "After the second week, in addition to the fact that the estimates are but few, the results are vitiated by the fact that the cases remaining in the hospital at so late a period were for the most part instances of severe fever of long duration, after which, as is shown by the first table, a much greater degree of anæmia is reached" (Thayer).

SHOWING THE HIGHEST AND LOWEST COUNTS IN EACH WEEK.

1st v	veek											 			Highest. 6,940,000	Lowest. 3,400,000
2d .	44											 			6,604,000	2,240,000
3d	66											 			6,916,000	2,300,000
4 th	66	,										 			5,884,000	1,426,000
$5 \mathrm{th}$	66											 			6,312,000	1,352,000
6 th	44											 			4,904,000	2,014,000
7th	66						 			,		 	,		4,500,000	1,648,666

In only one of these cases could the high count be explained as a concentration of the blood through diarrhea and vomiting, but counts made just after a bath are often very high owing to blood concentration.

<sup>&</sup>lt;sup>1</sup> Antipyrin and acetanilid have no effect on the red cells.

# Hæmoglobin.

Thayer's figures are as follows:

1st	week	of fever,	21	estimates	averag	e	76	per cent.
2d	44		50	66	46		73	+6
3d	46	"	32	44	66		67	"
$4  ext{th}$	66	66 6	20	66	44		60	44
5th	64	46	15	66	66		58	44
6 th	66	44	6	66	"		62	44
$7 \mathrm{th}$	66	44	4	66	46		50	46

Convalescence	1st	week,	22	estimates	average	 67	per cent.
46	2d	66	19	46	66	 69	46
44	3d	44	12	66	66	 67	44

This table shows a gradual decline during the febrile period, with a very slow regeneration in convalescence. The hæmoglobin (as in most secondary anæmias) suffers more than the count of corpuscles, and is slower in reaching the normal, so that the color index is low throughout (see chart on p. 202).

# Leucocytes.

Thayer records 832 estimates of the white cells in uncomplicated cases.

Based on one count per week in each case, the average being taken for the week in every case in which multiple counts were made.

1st v	veek	of fever,	100	counts	5.									6,400
2d	66	46	206	66										6,200
3d	44	46	150	66				 		 	 			5,700
$4 \mathrm{th}$	44	44	95	46										5,400
$5  ext{th}$	44	44 .	58	66						 	 			5,380
$6 \mathrm{th}$	66	44	19	66				 		 				5,800
$7 \mathrm{th}$	66	44	13	66				 		 	 			6,300
8th	44	44	.12	66						 				6,400

Thayer comments: "It would seem that the longer the disease lasts, the more profound the prostration, the lower the count." Ewing says: "The more severe the typhoid intoxication the lower the count." How great the variations may be even in the absence of any apparent complication is shown in the following table:

											Highest.	Lowest.
1st	week	of fever	 	 		 					15,000	1,600
2d	66	44	 		 	 	 ٠,				18,000	1,000
3d	. 46	. 66				 					13,000	1,000
$4  ext{th}$	46	66		 	 	 					10,500	1,700

														Highest.	L	owest.
5th	week	of fever				 						 		10,500	2	2,300
$6 \mathrm{th}$	66	46		٠		 			 	٠				10,000	٩	3,250
7th	66	46				 						 		11,000	4	1,000
8 th	66	46										 		 9,250	4	1,000
9 th	44	. 44	٠									 		9,300	2	000,

Most of these high counts were in the blood of one individual, who, throughout the disease, without any apparent reason, showed constantly a large number of colorless corpuscles. The count of 18,000 may have been after a cold bath, which Thayer has previously shown often raises the count of white cells.

In convalescence the count of leucocytes begins to rise toward the normal as the following table indicates:

1st we	ek of a	pyrexia	, 32	counts	S	 		 		 			6,000
2d	66	66	24	46				 		 			6,700
3d	44	46	16	46				 		 			6,300
4th	44	66	6	66			 	 					7,570

Thayer's results may be exhibited in the following chart (page 202).

In the majority of the one thousand cases recorded at the Massachusetts General Hospital, the course of the leucocytes from week to week has unfortunately not been followed with accuracy.

Most of our counts were made on the day of entrance to the hospital, presumably during the first or second week of the fever.

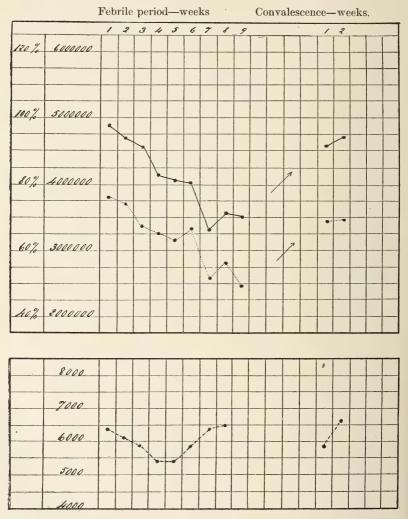
The range of the counts was as follows:

```
Between 1.000 and 2.000 = 10 cases.
         2,000 " 3,000 = 56
         3.000 "
                 4.000 = 135
         4.000 " 5.000 = 187
   66
         5,000 " 6,000 = 156
   66
         6.000 " 7.000 = 149
         7,000 " 8,000 = 112
   66
        8,000 " 9,000 = 78
         9,000 " 10,000 = 60
   66
        10,000 "
                 11.000 = 27
        11,000 " 12,000 = 19
        12,000 "
                 13,000 = 6
        13,000 " 14,000 = 3
                          2
        14,000 " 15,000
                        1,000 cases.
```

From these figures I have excluded all cases counted only under circumstances likely to concentrate the blood (cyanosis, after baths, after severe diarrhœa).

Of these cases 970 or 97 per cent had less than 11,000 leucocytes per cubic millimetre at the time of entering the hospital, and 69.3 per cent had less than 7,000.

CHART OF THE BLOOD IN TYPHOID FEVER.



Plain line = red cells. Dotted line = hamoglobin. Broken line = white cells.

But these figures, like those reported by Thayer and Türck, differ from the reports of some other observers in not showing so large a proportion of very low counts. Thus Khetajurow expects to find only 2,500 to 3,000 leucocytes in the third and fourth weeks, but our observations show that this is not a law.

# Complications.

Thayer's study of the effects of complications is by far the most thorough ever published.

1. Hemorrhage from the Bowels (11 cases). The red cells fall off markedly in one case from 3,648,000 (eighteen days before) to 1,992,000, in another to 2,000,000; yet the first of these cases recovered.

The leucocytes showed no appreciable change in half of these cases, while in the rest there was some leucocytosis (24,800 in one case, 17,400 in another, 10,500 in a third), reaching its maximum in from twelve to twenty-four hours, and returning to normal in from two to seven days.

2. Perforation of the Bowel (8 cases). Leucocytosis was well marked in three (16,400, 23,400, and 16,000), slight in two (10,400 and 11,200), and completely absent in three, at the time of the perforation. Theyer studied the clinical features of these cases and the results of cultures made at operation, and concludes: "It is probable that slight local peritonitis always produces . . . leucocytosis unless the individual is already in a condition of profound general septicæmia. On the other hand, a sudden (general) infection of the peritoneum with large quantities of excessively malignant organisms may often result in complete absence of leucocytosis or a relatively slight rise, followed later by a fall. Three cases of streptococcus peritonitis showed no leucocytosis at any time. The prospect of relief by surgical interference is best in those cases with a leucocytosis." Thayer also shows that a preperforative leucocytosis due to local peritonitis about deep ulcers may occur. He adds, however, a summary of four cases in which symptoms suggesting perforation and accompanied by leucocytosis led to a laparotomy, yet in which no perforation was found, the symptoms being due in one case to thrombosis of the left iliac vein, while in the others their cause was not found. In many of these cases the leucocytosis was very transitory, and without frequent (almost hourly) counts would have been overlooked.

In the series of cases of typhoid perforation reported by Shattuck, Warren, and Cobb (*Boston Medical and Surgical Journal*, June 28th, 1900) there are four cases of general peritonitis with no

leucocytosis (3,800, 5,400, 7,300, and 8,000), and four cases with leucocytosis (14,000, 16,000, 17,200, and 23,000). Two cases with leucocytosis (14,300 and 13,200) showed at operation a perforation protected by local adhesions. In most of these only one count is recorded, so that the observations are of little value.

There is no doubt that leucocytosis does occasionally occur when no complication exists so far as we can ascertain during life. Four of the cases over 11,000 (see the above table) were counted repeatedly and complications were carefully sought for, but none were found. The most striking case showed the following counts:

46	4th	
66	5th	
44	7th	
66	8th	
44	10th	
44	13th	
66	15th	
66	17th	

The autopsy showed typical typhoid lesions and nothing else.' Another and much milder case showed 11,000–12,000 white cells constantly for over two weeks, and no cause could be found to account for it.

The great rarity of such cases and constant association of leucocytosis with any of the numerous complications which we can recognize, rather inclines me to the belief that in all the cases in which leucocytosis exists constantly, some complication really is present though unrecognized. The possibility of a secondary septic infection, of an osteomyelitis, or phlebitis of internal veins is very difficult to exclude.

- 3. Furunculosis.—Thayer records 7 cases in all, of which the leucocyte count is very slightly raised when we compare it with that usually found in typhoid (e.g., 9,000, 10,000, 10,200, 10,600, etc.).
- 4. Thrombosis—6 cases in Thayer's study are of especial interest, because the leucocytosis with which each was associated appeared in 3 cases earlier than any of the localizing symptoms, such as pain and œdema.

The counts varied from 8,000 and 21,000 in femoral phlebitis

 $<sup>^{\</sup>rm 1}$  Thrombosis of internal veins and osteomyelitis were not carefully searched for at autopsy and may have existed.

to 24,800 in plugging of the iliac vein. I have had two similar cases.

5. Pleurisy—5 cases, all showed slight leucocytosis (10,000–12,000). Only in the purulent cases (empyema) was the count higher (23,000, 18,000). In one case the tapping revealed a bloody and purulent fluid containing only typhoid bacilli. After the tapping the leucocytes rose to 44,500.

In most of these cases the percentages of the different varieties of leucocytes was but little affected (e.g., 68 per cent of polynuclear cells and 1.8 per cent of eosinophiles with a count of 23,000 leucocytes. This is *not* an ordinary leucocytosis.

- 6. Pneumonia—5 cases, 3 with leucocytosis, 2 without it (terminal infections). Both of those without leucocytosis and 2 of the others proved fatal. The counts were 35,000, 38,000, 8,200, 4,000, and 6,000. The neutrophiles were not increased as much as in ordinary leucocytosis. Türck records a case with but 1,600 leucocytes despite lobar pneumonia, and Kohler mentions several similar cases.
- 7. Bronchitis (severe) and Broncho-pneumonia—4 cases, 3 showed leucocytosis (16,600, 17,200, 18,200).
- 8. *Periostitis*—3 cases with leucocytosis reaching 22,000, 17,600, and 13,000 (only 72 per cent of polynuclear cells in first case).
- 9. Submaxillary Abscess (streptococcus) with a maximum count of 18,200 which developed late in the course of the process. In another case with perforation peritonitis, the submaxillary abscess (staphylococcus and typhoid bacillus) did not produce any rise in the leucocytes.
- 10. Otitis Media—2 cases with leucocytosis of 15,600 and 11,-800 (maximal). I have had 10 cases with maximal counts of 16,400, 14,000, 11,200.
- 11. Parotitis—3 cases, no leucocytosis in 2; in the other 30,-500 (general infection with the staphylococcus aureus found at autopsy.
- 12. Perirectal Abscess—25,100 leucocytes. In one of my cases (moribund) a large ischio-rectal abscess developed without producing any leucocytosis.
  - 13. Pericarditis (dry)—11,500 leucocytes.
  - 14. Bed-Sores (3)—16,000 leucocytes (average).
- 15. Conjunctivitis—9,330 lucocytes (polynuclear cells 74 per cent.

- 16. Cholecystitis—3 cases, all showing leucocytosis; 28,500, 21,200, and 14,400 (maximal).
  - 17. Cystitis 3 cases, 1 with marked leucocytosis; 18,000.
- 18. *Urethritis*—3 cases, 1 with 13,700 leucocytes, of which 5.5 per cent were eosinophiles.
- 19. Tuberculosis (pulmonary)—1 case with 14,200 leucocytes, of which only 55 per cent were polynuclear. Türck records a similar case with a normal leucocyte count. Pregnancy and peripheral neuritis seemed to have no especial effect on the blood.

# Qualitative Changes.

Red Corpuscles.—Turck notes "the relatively frequent presence of marked differences in the size of the red cells with very numerous dwarf forms; occasionally poikilocytosis and polychromatophilia," i.e., the changes common to all varieties of secondary anæmia.

White Cells.—Thayer's extensive and painstaking studies are exhibited in the following table:

	Counts.	Polymorpho- nuclear neutrophiles, per cent.	Small mono- nuclear, per cent.	Large mono- nuclear. per cent.	Eosinophiles, per cent.
First week of fever	12	74	13	12	0.5
Second " "	39	71	14	13	0.8
Third " "	34	66	21	11	0.3
Fourth " "	19	65	20	14	0.4
Fifth " "	8	62	18	19	0.3
Sixth " "	4	58	22	13	6.0!
First week apyrexia Second " " Third " "	12 7 6	61 49 57	21 31 15	15 17 23	3.0 2.3 3.5

Table XII.

These averages, however, cover up some aberrant percentages. For example, there was one case which in the first week showed 15,000 leucocytes, of which 92.3 per cent were polymorphonuclear neutrophiles. No complication could be found. The lymphocytes were but 7.7 per cent, and the eosinophiles had altogether disappeared. Nine days after defervescence the leucocytes were 9,000, with 48.3 per cent of neutrophiles, 43.1 per cent lymphocytes, while the eosinophiles had risen to 8.6 per cent.

High percentages of polymorphonuclear neutropiles sometimes occurred without an increase in the total count, e.g., in the second

week a case with 8,000 leucocytes, of which 94.4 per cent were polymorphonuclear, and in the third week a case with 4,000 leucocytes, of which 82 per cent were polymorphonuclear.

In the ninth week one case showed 12.7 per cent of eosinophiles with 70.4 per cent of polymorphonuclear neutrophiles.

Summing up Thayer's observations, we find:

- 1. A steady diminution in the polymorphonuclears, the lowest point being reached at the end of the pyrexia. This is an absolute diminution.
- 2. A relative increase in the lymphocytes, especially the larger forms; absolutely their number is not much changed.
- 3. A reduction (relative and absolute) of the eosinophilic cells during the pyrexia followed by an increase in convalescence, which may amount to a considerable eosinophilia.

Türck's results are practically the same. He adds that eosinophiles may actually disappear from the blood at the height of the disease, and considers that their reappearance or increase previous to defervescence augurs a relatively short course for the fever, and (aside from the occurrence of complications) a good prognosis. Myelocytes and *Reizungsformen* were occasionally present in his preparations, even in a case with a leucopenia of 4,200 and but 52 per cent of polymorphonuclear neutrophiles.

# Summary.

- 1. The red cells suffer to the extent of about 1,000,000 in the course of an average case, the reduction taking place gradually, and being most marked at the end of defervescence in most cases. Sweating, vomiting, or diarrhœa may cause considerable transient elevation in the count of red cells, while sudden losses follow intestinal hæmorrhage. Occasionally a very severe post-febrile anæmia occurs, the red cells being reduced nearly to 1,000,000 with the qualitative changes of a grave secondary anæmia. In most cases the qualitative changes are slight.
- 2. Hæmoglobin, as in most anæmias, suffers somewhat more than the number of red cells.
- 3. The number of leucocytes is subnormal throughout the disease, averaging about 5,000 at its height, though much lower figures are common. This leucopenia progresses with the severity and duration of the infection. Cold baths cause an immediate transient increase in the number of leucocytes in the peripheral circulation,

an increase which may amount to double or triple the number before the bath.

Differential counts show, during the febrile period, a progressive diminution in the number and percentage of the polynuclear cells, with a corresponding rise in the percentage of lymphocytes and large mononuclear cells, and a great diminution or even disappearance of the eosinophiles. In convalescence the percentage of eosinophiles markedly increases, often before the other forms have resumed their normal numbers.

4. Most complications, especially inflammations, produce a leucocytosis, but a particularly malignant infection may be followed by no increase and even by a diminution in the number of leucocytes. In many of the leucocytoses following complications the percentage of polymorphonuclear cells does not rise.

# Diagnostic Value.

There are few diseases (outside of those known as diseases of the blood itself) in which the blood count is so often of value in diagnosis. The diagnosis of typhoid fever is made by exclusion—exclusion of other causes of fever and of local inflammatory processes in particular.

1. In this process of exclusion, the blood is a most powerful adjuvant, inasmuch as almost all local inflammatory processes have leucocytosis, while typhoid (uncomplicated) does not. I recall two cases in which the chart and symptoms pointed to typhoid, but in which the persistent marked leucocytosis directed attention to the search for an inflammatory focus. Both were at first unattended with pain, tenderness, or other localizing symptom, but later signs and symptoms began to point to the liver, from which pus was evacuated by puncture. These cases of abscess of the liver are typical of the value of blood examination for any deep-seated suppuration. I have seen good clinicians puzzled for twenty-four hours over the diagnosis between appendicitis and typhoid, but the indication of the blood count was always fulfilled. Pyæmic or septicæmic processes are usually distinguishable from typhoid by the same test—the presence of leucocytosis in the former.

Of the value of the blood in distinguishing certain cases of pneumonia from typhoid I have already spoken on p. 195.

2. Aside from local or general pyogenic infections perhaps the disease most often confounded with typhoid is *malaria*. This is

especially the case in the southern part of this country, where for want of proper blood examination the confusion of the two diseases is indicated in such a term as "typho-malarial fever." Malaria and typhoid are alike in having no leucocytosis, but the presence of the malarial parasite is an absolute test and in marked cases is always decisive. Very mild cases of malaria may show so few organisms in the peripheral circulation that without prolonged search they cannot be found, and in the severest types of all, the organisms are not very abundant. In the vast majority of cases, however, the organism can be readily found and our diagnosis made certain.

3. Tuberculosis, local or miliary, if uncomplicated by any pyogenic organisms, cannot be distinguished from typhoid by the blood count alone, as neither disease shows leucocytosis, but here the Widal reaction (see p. 458), comes to our rescue.

A large proportion of lymphocytes is commoner in typhoid than in tuberculosis, but it may occur in either disease. In the majority of cases, however, tuberculosis is complicated with septicæmia from a secondary pyogenic infection, and is then easily distinguished by the existence of leucocytosis.

- 4. Typhus fever has not been well studied and the reports of its blood condition are contradictory. At present we cannot say whether or not it can be distinguished from typhoid by the blood examination. In most cases the absence of a serum reaction will exclude typhus.
- 5. Two cases of erythema nodosum with fever between 101° and 103° gave me trouble in diagnosis lately. In both the blood was normal and differed from typhoid only by the absence of a serum reaction. Thayer has reported a similar case (*loc. cit.*, p. 530), in which, however, there was a marked leucocytosis throughout.
- 6. Trichiniasis may run a course quite indistinguishable clinically from that of typhoid, but the presence in trichiniasis of a leucocytosis with marked eosinophilia and the absence of Widal's reaction will decide any ease of doubt.
- 7. Most auto-intoxications (ptomain poisoning) produce leucocytosis, and can therefore be distinguished from typhoid.
- 8. Meningitis, especially in its epidemic cerebro-spinal form, has many symptoms like those of typhoid, but it always produces leucocytosis, and is never associated with Widal's serum reaction.
  - 9. From influenza typhoid cannot be distinguished by the blood

count, as neither of them produces leucocytosis. Here the blood gives aid only through the serum reaction.

10. Acute Infectious Dysentery may present (especially in the tropics) many features that remind us of typhoid. As a rule it produces no leucocytosis, but it is distinguishable from typhoid by the presence of Widal's reaction in the latter.

The occurrence of complications in typhoid may mask its characteristic blood changes so as to make the blood useless in diagnosis; but in most early cases, in which the diagnosis is especially important and difficult, the blood shows no leucocytosis and is therefore of great value in the exclusion of other diseases.

## Prognosis.

In prognosis Naegeli (Deut. Arch. für klin. Med., vol. lxvii., p. 279) agrees with Türck in regarding the persistence or early reappearance of eosinophiles as a favorable sign, and believes that a normal number of polynuclear cells is a good sign when the outlook is more serious, if the leucocyte count is very low and does not increase during complications.

### DIPHTHERIA.

Bacilli of diphtheria in the circulating blood are practically never to be found.

The specific gravity, according to Grawitz, is *above* normal at the height of the disease. He obtained the same result experimentally by injecting cultures of the Klebs-Löffler bacillus into dogs and rabbits. He concludes that the poison of the disease is lymphagogic and so concentrates the blood.

Red Corpuscles.—Morse's investigations show an average of 5,100,000 in twenty cases counted during the first week of the disease and of 5,150,000 in 10 cases during the second and third week of the disease—practically normal figures.

These are the first systematic<sup>2</sup> investigations of the red cells in diphtheria and are confirmed by the reports of Ewing, Engel, and Billings. The latter observer in counts made in seven cases during the first five days of illness found an average of 5,600,000+ red cells per cubic millimetre. During the first five to ten days after

<sup>&</sup>lt;sup>1</sup> Boston Medical and Surgical Journal, March 7th, 1895.

<sup>&</sup>lt;sup>2</sup> Earlier reports are faulty as to technique.

this, the same cases showed an average loss of 510,000 cells per cubic millimetre; five out of the seven showing considerable losses, two remaining about the same. These were cases treated without antitoxin. The two cases showing no loss of red cells were both very mild, one having no membrane at any time. The diminution ranged from 470,000 (third day) to 2,040,000 (sixth day). As a rule no diminution can be made out until after the third or fourth day.

Out of twenty-three cases treated with antitoxin and each counted several times over, only three showed any considerable diminution in the red cells and these lost less than 400,000 each, not much beyond the limit of error (200,000) allowed for by the investigator, and all of them severe cases. Six patients who were anæmic when admitted (average=4,640,000) showed a steady rise in the red cells as the disease (treated with antitoxin) progressed.

It is evident from these figures that antitoxin largely prevents the anæmia which usually develops in the first five to ten days. In cases not treated with antitoxin the regeneration from the resulting anæmia is slow. Healthy individuals injected with antitoxin showed a very moderate reduction in the red cells in about one-half the cases, the greatest loss being 932,000 per cubic millimetre (fifteen cases counted by Billings).

Qualitative Changes.—Billings' careful study of stained specimens showed no deformities in size or shape and no nucleated red cells, but Engel has found normoblasts. Polychromatophilic red corpuscles were very few in the cases in which antitoxin was used, but more numerous when it was not used.

Hæmoglobin.—Here again the most thorough investigations are those of Billings. In cases treated without antitoxin there was an average loss of ten per cent, regained in part during convalescence, but as usual reaching normal later than the count of corpuscles. When antitoxin was given, the diminution of hæmoglobin was less marked, but when the decrease did occur the return to normal was slow compared to that of the red cells, even when the patients were up and about and apparently well.

White Corpuscles.—Leaving out the older observations in which the technique was probably faulty, the principal investigators are Morse, Ewing, Gabritschewsky, Billings, Filé, and Engel.

All agree that a considerable leucocytosis is present in most cases—34 out of 36 of Billings' cases, 26 out of 30 of Morse's (the latter

made but one count in each case), 49 out of 53 of Ewing's. In a general way, the severest cases show the greatest leucocytosis, but it does not follow the pulse, temperature, nor the extent of the membrane, and "the ordinary clinical examination of the patient is of much greater value in . . . prognosis . . . than any information to be gained from the examination of the blood. The latter is simply confirmatory, never indispensable" (Billings). Morse's conclusions are the same, although he considers that with notable exceptions the amount of membrane is a rough measure of the degree of leucocytosis. He finds no correspondence between the glandular swellings and the degree of leucocytosis, though he noted that "in the fatal 'septic' cases with greatly enlarged glands," very high counts were present. Other cases with little or no enlargement of glands showed equally high counts, however.

Ewing's 4 cases without leucocytosis were all mild, but of Billings' 2 cases without leucocytosis one was the severest of his whole series, while the other was mild. Of Morse's 4 cases without leucocytosis 3 were mild and 1 was severe. Gabritschewsky's 14 cases all showed leucocytosis.

Putting the results of these four observers together we see that when leucocytosis is absent the cases are *either* very mild or very severe, conditions analogous to those to be noted in pneumonia and septicæmia. The counts in recent epidemics range from normal to 48,000 (Morse) or to 38,600 (Billings). Felsenthal ' found 148,229 per cubic millimetre in one case, and Bouchut's counts are often over 75,000.

In a general way the counts rise while the disease progresses and fall gradually as improvement goes on, disappearing after the membrane. "The leucocytosis is well marked by the third day and very likely earlier" (Morse). Billings found an increase after one day's illness, but usually less than was present later in the disease; one of his cases, however, had a higher count on the first day of the disease than on any subsequent day, though no antitoxin was given.

The injection of antitoxin has apparently no effect upon the leucocyte count (strange to say) except in the first twenty-four hours after its use. Immediately, *i.e.*, within thirty minutes after an injection, the leucocytes are stated by Ewing to be considerably

<sup>&</sup>lt;sup>1</sup> Archiv f. Kinderheilk., vol. xv., p. 78, 1893.

<sup>&</sup>lt;sup>2</sup> Comptes Rendus, 1877, lxxv., No. 3.

diminished, but the leucocyte curve does not reach normal any sooner than in cases in which no antitoxin is given, although it begins to fall in the majority of cases after the injection. The same thing (according to Billings) takes place without antitoxin.

The leucocytes of healthy persons are likewise unaffected by antitoxin injections.

Qualitative Changes.—All authors agree that in most cases the neutrophiles are increased. Morse found an average of 80 per cent in 26 of his 30 cases. Of the other 4, 1 was normal and 3 were subnormal (58, 59, and 59 per cent); 2 of these were convalescent, the other had been sick a week and had 12,000 white cells per cubic millimetre. A marked lymphocytosis was present in 2 of Ewing's 53 cases, 43,200, and 13,950 absolute. In Billings' cases the polymorphonuclear varieties averaged 80 per cent and the lymphocytes 19 per cent, the eosinophiles being reduced to 1 per cent on the average and often being entirely absent. With Morse eosinophiles averaged 2 per cent.

The proportion of polymorphonuclear cells is usually directly proportional to the total increase of leucocytes.

Ewing thinks that "the staining reaction of the leucocytes is an accurate measure of the severity of the diphtheritic infection," and this staining reaction he finds increased in favorable cases by the injection of antitoxin.

Billings did not find any such changes in "staining reaction," though he claims to have carefully followed out Ewing's procedures.

Engel<sup>2</sup> found that antitoxin at first slightly increased the percentage of lymphocytes, and sometimes this increase was very marked. In one case the lymphocytes increased from 24 to 65 percent after antitoxin.

The point on which he specially insists is the presence of considerable numbers of *myelocytes* in fatal cases.

Of the patients examined by him 17 died, and 9 of these had from 3.6 to 16.8 myelocytes in every one hundred leucocytes. Myelocytes were also present in some of the patients who recovered, but in smaller numbers (1.3 to 1.5 per cent).

In one case he found on the third day of the disease 4.3 per cent of myelocytes, and from this point the percentage gradually rose to

<sup>&</sup>lt;sup>1</sup> In a case of Rieder's, aged three years, the lymphocytes rose from 19 per cent during the fever to 64 per cent in convalescence.

<sup>&</sup>lt;sup>2</sup> Gesellsch. f. innere Med., Berlin, July 6th, 1896.

13.8 per cent, and then fell, there being 1.7 per cent present at the time of death. An abscess occurring in the case showed only the usual polymorphonuclear leucocytes in its contents. He concluded that a large percentage of myelocytes is a bad prognostic sign in any case.

Myelocytes are not mentioned in any of the numerous differential counts made by Gabritschewsky, Ewing, Morse, and Billings, so that Engel's observation is so far unique.

## Summary.

- 1. Moderate anæmia, especially in cases treated without antitoxin. Regeneration is slow.
- 2. Leucocytosis, very roughly parallel to the severity of the disease, unaffected by antitoxin treatment, gradually decreasing as the disease passes off, sometimes absent in very mild or very severe cases.
- 3. Polymorphonuclear leucocytes much increased during febrile stages, often diminished in convalescence.
  - 4. Myelocytes numerous in some severe cases.

The blood examination has no diagnostic value so far as I can see; in prognosis the absence of leucocytosis (except in obviously mild cases) and the presence of many myelocytes are apparently bad signs.

## CHAPTER IV.

## ACUTE INFECTIOUS DISEASES (CONTINUED).

### SCARLET FEVER.

Heubner' noted hæmoglobinæmia in one case. Fibrin is not increased even at the height of the fever, provided inflammatory complications are absent.

Red Cells.—Very little is to be found in literature upon the subject. Kotschetkoff onted a gradual diminution of the red cells to about 3,000,000, regeneration taking place in the course of not less than six weeks. Other observers have found little or no anæmia.

Hayem<sup>3</sup> estimates the average loss of red cells at 1,000,000. In mild cases he finds the lowest figures on the first day of normal temperature. In severer cases in which the fever comes down slowly, the red cells may not reach their minimum till twenty-four hours after the normal temperature is regained.

Felsenthal in six cases found the count to be 4,500,000 to 5,500,000—no considerable variation from normal.

Zappert is in six cases found it to be from 3,920,000 to 4,500,000, an average of 4,150,000. Normoblasts are occasionally seen—as in one of Türck's cases, and the normal variations in size and shape are exaggerated.

White Cells.—Most observers are agreed that leucocytosis is the rule, contrasting in this respect with measles, in which no leucocytosis occurs. The increase may be present even six days before the rash appears and attains its maximum two or three days after the eruption. In light cases it may sink to normal even before the fever is gone, while in severer cases it may persist several days after normal temperature is reached. Von Limbeck had a case in which

<sup>&</sup>lt;sup>1</sup> Deut. Arch. f. klin. Med., vol. xxiii.

<sup>&</sup>lt;sup>2</sup> Ref. in Petersburg. med. Woch., 1892, 1.

<sup>&</sup>lt;sup>3</sup> Loc. cit., p. 914.

<sup>&</sup>lt;sup>4</sup> Arch. f. Kinderheilk., 1892, p. 80.

<sup>&</sup>lt;sup>5</sup> Zeit. f. klin. Med., 1893, p. 292.

the leucocytosis persisted for twelve days after the temperature had become normal. Forty thousand per cubic millimetre is not unusual in well-marked cases. Rieder's ten cases averaged 17,500; Felsenthal's six counts were between 18,000 and 30,000. My own are similar.

In a general way the severest cases are apt to have the highest leucocyte counts; the figures have no direct relation to the amount of fever, glandular swelling, or to complications in the ear or kidney.

Qualitative Changes.—The polymorphonuclear forms are increased, often to 90 per cent, soon falling except in the worst cases. The peculiar characteristic of the disease is the persistence of eosinophiles in all but the severest cases despite the increase of polymorphonuclear forms. The only other infections of which this is true are tetanus and acute articular rheumatism. They may run as high as 5 per cent during the fever, and are still more numerous in convalescence, remaining increased for six weeks. According to Kotschetkoff, disappearance of eosinophiles is a bad prognostic sign except at the very beginning of the fever, when they may be temporarily absent in favorable cases. Presumably they have some connection with the exanthem, eosinophilia being so common in connection with skin lesions. They may number 15 to 20 per cent of the leucocytes in convalescence (Bensaude). Türck reports 14.3 per cent (1,800 absolute) in one case and 13.3 (800 absolute) in another. Felsenthal's average is 5 per cent; Zappert's, 3 per cent. The lymphocytes are decreased proportionately to the severity of the case, the worst cases showing only 2 to 4 per cent.

An increase of eosinophiles during a scarlatinal nephritis is regarded by Neusser and his pupils as a favorable sign, and their absence as ominous. In ordinary cases without nephritis they reach their maximum in the second or third week and are not normal till the sixth. In the active stages of the disease myelocytes, transitional neutrophiles, and "stimulation forms" occur.

## Summary.

Moderate anæmia.

Leucocytosis beginning before the eruption and often lasting into convalescence.

Eosinophiles said to be increased in favorable cases, absent in bad cases.

## Diagnostic and Prognostic Value.

- 1. The chief importance of the blood examination is in distinguishing the disease from measles and the eruptions of other diseases. Measles has no leucocytosis.
- 2. Whether the prognostic significance attached by Neusser and others to the percentage of eosinophiles is genuine or not, cannot as yet be positively stated.

### MEASLES.

In mild cases the blood shows no changes at all. When bronchitis, coryza, and conjunctivitis are very marked, fibrin may be increased.

Red Cells.—In mild cases no change—never over 400,000 or 500,000 red cells are lost (Hayem). Felsenthal's eight cases showed counts of 5,000,000 to 5,500,000.

White Cells.—There is no leucocytosis, often a leucopenia during the eruptive stage. In convalescence the lymphocytes and especially the large mononuclear forms are increased. Felsenthal in eight cases found the count normal or diminished. Pée found but 4,000 in a case with a fever of 102.7°. Rieder's eight cases averaged 7,500, being lowest at the height of the disease and increasing as fever passed off. Complication with catarrhal pneumonia or a very bad bronchitis and coryza, may slightly raise the count. The eosinophiles, contrary to the example of scarlet fever, are often diminished during fever.

The Massachusetts General Hospital records furnish the following counts:

TABLE XIII.—MEASLES.

	TABLE ATT.—MEASLES.											
Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.							
4 11 38 8 21 23	 М. М.	4,700,000	11,000 10,100 9,000 9,000 8,200 8,000	65  68	Rash out; temp. 104°.  "Black measles"; petechiæ. Differential count normal. Rash out; temp. 103°. 104°; eruption out.							
4 10	M. M.	5,000,000	7,000 6,000 6,000 6,000	60	Eruption just out. 103°; three days before the eruption; differential count normal. Eruption out one day. Eruption out three days.							
53 33 14	F. F.		3,500 3,500 1,400	67								

Felsenthal found the polymorphonuclear cells much increased and eosinophiles never over one per cent. In my own cases the differential counts were normal. The *value* of the blood examination is considerable in excluding scarlet fever, diphtheria, and syphilitic roseola, all of which show leucocytosis. It cannot apparently be distinguished by the blood count from *rötheln* (German measles), in two cases of which, seen at the Massachusetts General Hospital, the white cells were 6,000 and 8,000 respectively.

### MUMPS

Five cases of *mumps* under my care showed no leucocytosis. Türck on the other hand records one case with marked leucocytosis. Data are very scanty regarding the disease.

### WHOOPING-COUGH.

Meunier (Archiv. d. Maladies de l'Enfance, April, 1898) reported studies in 102 cases of whooping-cough. Lymphocytosis is early and constant. The counts averaged 22,700 in the cases examined during the catarrhal stage and before the advent of typical "whooping" paroxysms. In the paroxysmal stage the leucocytes average 40,000—the maximum being 51,250. In infants under four years the leucocytosis is far more intense than in older children. After the fourth year the count runs from 12,000 to 18,000. All the varieties of leucocytes are increased, but the lymphocytosis perhaps due to stimulation of the bronchial lymph glands.

Meunier found no such changes in the blood of cases bronchitis or tracheitis, and suggests that the blood count may be of use in the investigation of doubtful epidemics in schools or hospitals.

The following case exemplifies these rules (see also p. 195).

Age.	Red cells.	White cells.	Per cent hæmoglobin.	
3	5,192,000	75,000	47	July 23d.
				Polynuclear, 42. Lymphocytes, 57.
				Eosinophiles, 1.
		26,500		August 19th.
				August 31st. Polynuclear, 56.
				Lymphocytes, 43.
~				Eosinophiles, 1.
5		32,800		Lymphocytes, 69.

TABLE XIV.—WHOOPING-COUGH.

These results have been confirmed by De Amicis, Cima, and others.

### SMALLPOX (VARIOLA).

Red Cells.—According to Hayem no other fever is so destructive of red cells. During the fever the count is normal or increased, but when the temperature falls permanently the number of red cells falls suddenly, whether because the blood is diluted (see above, p. 188) or by a real destruction. From this time on the cells are slowly regenerated; even at the fifteenth day Hayem found them considerably below normal.

In hemorrhagic cases the anæmia comes on more quickly, its degree depending on the amount of hemorrhage. In one patient, dying on the seventh day of the eruption, Hayem found but 2,000,-000 red cells, in another at the same stage, 4,600,000.

Fibrin is not increased until the stage of suppuration is reached.

## Leucocytes.

In Pick's report on 42 cases no leucocytosis is recorded until the appearance of vesicles.

Elaborate studies in the blood of smallpox have lately been published by Weil,¹ and by Courmont and Montagard.² These studies are concerned especially with the leucocytes. In Weil's series of 36 cases the counts ranged between 6,000 and 10,000 in 6 cases, between 6,000 and 13,000 in 13 cases, exceeding 15,000 in 9 cases, exceeding 20,000 in 3 cases, 25,000 in 3 cases, 30,000 in 1 case, 35,000 in 1 case.

One case ranged from 3,000 to 6,000 during the whole course of the disease, except on the day of vesiculation (24,000), but this is very rare, and the leucocytes are usually increased from the beginning. The increase is usually most intense at the time of vesiculation and from that time does not vary notably until after pustulation, when it slowly declines until in convalescence a subnormal count is reached. In hemorrhagic cases the increase is usually less marked.

A sudden drop in the leucocyte count may occur in the fatal suppurating or hemorrhagic forms. For example, in 2 fatal suppurating cases the leucocytes dropped from 24,000 and 18,000 to 6,200. In one hemorrhagic case on the dying day counts of 6,200,

<sup>&</sup>lt;sup>1</sup> Soc. de Biol., June 29th, 1900.

<sup>&</sup>lt;sup>2</sup>Soc. de Biol., June 22d, 1900; July 6th, 1900.

6,000, and 4,400 were recorded. A sudden drop in the leucocytes is then a bad prognostic sign (from this opinion Courmont and Montagard dissent).

Complications occurring in convalescence produce a second rise in the leucocytes.

## Qualitative Changes.

The most significant fact in the blood of variola, according to the writers already quoted, is the increase in mononuclear cells. The percentage of polynuclear cells, instead of being increased as in most infectious diseases, is from the outset diminished (i.e., 40 to 50 per cent), and may go as low as 14 to 20 per cent. Eosinophiles range from normal (1–3 per cent) at the beginning of the disease, downward. They are lowest just before desquamation. In convalescence they are often slightly increased.

Among the "mononuclear cells" the increase of which is held by Weil to be characteristic of the disease are:

- (a) Small lymphocytes, 30-40 per cent.
- (b) Large mononuclear, 4-10 per cent.
- (c) Myelocytes, 2-10 per cent (even 25 per cent in hemorrhagic cases).
  - (d) Türck's "Reizungsformen," 2-10 per cent.

During suppuration and desiccation the mast cells are sometimes increased (5 per cent). The abnormal leucocytes—(c) and (d) above—are present from the very beginning of the disease and form a very characteristic part of the blood picture. They persist through pustulation and diminish only in convalescence. They are present in mild varioloids as well as in severe variola. Complications (pneumococcus or streptococcus septicæmia) do not materially modify the blood picture, unless they occur late in convalescence. In convalescence a polynuclear leucocytosis may result from suppurative complications.

# Diagnostic Value.

In excluding scarlatina, measles, purpura, syphilis, erythema multiforme, the blood is conclusive. Varicella, on the other hand, produces changes in the blood, which are precisely of the same type as those of variola, though less in degree.

### Vaccinia.

The red cells and hæmoglobin show no constant variation after vaccination (Sobotka), but the leucocytes are always increased, the

leucocytosis appearing in two waves,—one (varying from 12,000 to 23,000) which occurs from the third to the seventh day, and a second on the tenth to twelfth days (10,000 to 17,500).

### VARICELLA (CHICKEN-POX).

The only observation of which I am aware is that reported by Engel. In a child of five he found during the height of the pustular stage a moderate leucocytosis, with 67 per cent of neutrophiles (high for a young child), and no eosinophiles. Three days later, as the pustules were healing the neutrophiles had sunk to 47 per cent (normal for that age) and the eosinophiles had risen to 16 per cent.

### ACUTE ARTICULAR RHEUMATISM.

According to Hayem and Garrod <sup>2</sup> the blood constitutes, as in syphilis, a most valuable measure of the intensity of the sickness, which is parallel to the severity of the blood-changes rather than to the number of joints affected. The fever, the intensity of the lesions, and the state of the blood run parallel, in a general way, but the degree of anæmia is a more delicate index of the patient's condition than even the temperature chart (Garrod).

### The Blood as a Whole.

Fibrin is greatly increased. In no other disease except in pneumonia is the network thicker or more rapid in formation. According to Maclagan, this is to be explained by an increase of tissue metamorphosis. Coagulation, on the other hand, is not quicker, but slower than usual.

Lactic acid is present in excess, but cannot be clinically estimated, nor is its excess peculiar to this disease.

The alkalinity of the blood had been reported diminished, but the technique is not considered reliable by the best observers.

Red Cells.—Hayem<sup>3</sup> and Osler<sup>4</sup> state that the poison of acute rheumatism is a powerful and rapid destroyer of red cells. In acute cases, according to Hayem, the red cells lose at least 1,000,000 of their number, and in cases which drag along and relapse the loss is

<sup>&</sup>lt;sup>1</sup>15th Cong. für innere Med., 1897.

<sup>&</sup>lt;sup>2</sup> British Medical Journal, May 28th, 1892.

<sup>&</sup>lt;sup>3</sup> Loc. cit., p. 917. <sup>4</sup> "Practice of Medicine," 1895.

from 1,500,000 to 2,000,000. When an attack is cut short by salicylate treatment the drain on the corpuscles is stopped. Türck's careful studies led him to the same conclusions. Red cells and hæmoglobin are always markedly diminished during the fever, the hæmoglobin especially, and after the attack a post-febrile anæmia of varying severity is always left.

So far as my experience goes, this diminution does not seem to occur in all cases. Many of my cases had been sick some weeks before the time when the count was made, yet the counts are not very low. The average count of red cells in the whole group of cases is 4,300,000. The lowest counts were 2,528,000 with 45 per cent of hæmoglobin, 3,248,000 with 45 per cent of hæmoglobin, 3,456,000 with 50 per cent of hæmoglobin, 3,332,000 with 45 per cent of hæmoglobin, 3,468,000 with 36 per cent of hæmoglobin, 3,440,000 with 26 per cent of hæmoglobin, 3,608,000 with 40 per cent of hæmoglobin. Only 13 cases below 4,000,000 are recorded out of 113. According to Hayem, 4,000,000 is the usual count in acute cases and 3,000,000 to 3,500,000 in those which drag on and relapse.

Qualitative Changes.—Maragliano's so-called degenerative changes in the red cells have been observed in this disease, but are not very marked. Türck found erythroblasts in about a quarter of his cases. Deformities in the red cells are usually slight.

Hæmoglobin.—As in all secondary anæmias the corpuscles get thin and pale before they die, and hence the coloring matter is diminished more than the count. The average hæmoglobin percentage in this series is sixty-three, and the color index .73. Hayem noted that, in some cases during convalescence, as the red corpuscles slowly increase the color index remains low or even goes lower still.

Leucocytes.—All observers agree that leucocytosis is the rule and that its degree is roughly parallel to the acuteness and severity of the attack (the individual's vigor of reaction is always a factor) and the amount of fever. Türck insists that complications (pneumonia, pericarditis, pleurisy) are present whenever the count rises over 20,000, and in this he is supported by Ewing. No such complications were discovered in the 22 cases of Table XV., B, which exceed 20,000, but this table shows that in 80.5 per cent of 113 cases the leucocytosis was under 20,000. The following tables illustrate the variations of the leucocytes in a fairly typical way:

TABLE XV., A.—ACUTE ARTICULAR RHEUMATISM.

=								
No.	Age.	Sex.	Duration.	Degree of inflammation.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	21	M.	5 weeks.	?	4,160,000	31,500	65	Knees and one ankle.
1 2 3	20		o weeks.		3,832,000	27,800	45	ithees and one anale.
3	59	F.	?	?	5,476,000	27,000	94	Patient pale.
4 5 6 7 8 9	20	::	?.	?	4,392,000	26,000	50	
5	33	M.	2 weeks.	Red and hot	4,852,000	24,500	76	
7	Adult. 19	М.	5	2	4,218,000 3,248,000	21,000 $20,000$	56 45	Died.
8	7		?	į.	4,184,000	19,800	60	Died.
9	23		?	?	3,792,000	19,600	45	Third day.
10	23	Μ.	4 weeks.	Tender and hot	5,192,000	18,300	70	Temperature, 102°.
11	49	М.	?	3	4,800,000	17,700 17,400	55	Paronychia also.
12 13	46	F.		Red and hot	4,934,000 3,944,000	17,400	45	Chooles room
14	21 37	r.			5,224,000	16,300	58	Cheeks rosy.
15	24	M.	2 days.	3	4,600,000	16,000	68	
16	32				4,832,000	15,800	57	
17	13	F.	1 day.	Red and hot	4,880,000	15,200	65	Temperature 102°.
18	12	М.	2 weeks.	Red and hot	4,400,000	15,000	56	
19 20	$\frac{8}{20}$			• • • • • • • • • • • • • • • • • • • •	3,972,000 4,872,000	15,000 15,000	50 58	
21	22	• •			5,336,000	15,000	30	
22	19.	m.	4 days.	Red and hot	[4.760,000]	14,500	75	Severe case.
22 23	41				4,397,000	14,500	40	Seventieth day.
24 25	9	F.			4,210,000	14,386	60	
25	47	М.	1 day.	Red and hot	4,750,000	14.000	75	
26 27	25 18	F. F.	3 days. 2 months	Tender and hot No redness or	4,850,000 4,156,000	14,000 14,000	72 54	
21	10	г.	a months	heat.	4,100,000	14,000	94	
28	19	M.			4,172,000	14,000	70	
29 30	19	Μ.			4,580,000	13,500	64	
30	29				4,720,000	13,200	65	
31	30	• •			3,456,000	13,000	50	
33	32 29	M.			5,440,000 4,320,000	$12,800 \\ 12,750$	55 68	
34	20	M.			4,128,000	12,650	65	
35	37	F.	1 month.	Swollen and ten- der.	5,320,000	12,500	65	
36	30	F.			4,160,000	12,000		
37	47	Μ.	4 weeks.	Very slight	4,288,000	12,000	65	
38 39	27	F.	3 days.		3,580,000	11,600	65	
<b>4</b> 0	17	M. M.	1 week. 10 days.	Hot and red	4,600,000 4,200,000	11,500	70 60	
41	27 28			not and red	4,888,000	11,500 11,300	50	
42	33	M.	4 weeks.		5,480,000	11,000	80	Hands alone involved.
43	42				3,882,000	10,400	45	
44	33				4,056,000	10,200	50	
45	26	• •			4,728,000	9,400	40	35/3
46	$\frac{10}{20}$	F.			4,312,000 3,468,000	9,100 9,000	45 33	Mitral regurgitation.
48	36	F.			4,716,000	8,000	50	
49	28	M.	3 weeks.		3,608,000	7,000	40	
50	Adult.	Μ.			3,768,000	6,800		
51	29	Μ.	9 weeks.	Some joints hot	4,104,000	5,500	58	Fourth relapse.
52 53	30	F.			3,440,000	4,700	26	Specific gravity, 1.040.
54	28 14	• •			4,412,000 4,240,000		60 46	
55	23				2,528,000		45	Twenty-second day.
					,,		1	
-								

## TABLE XV., B.—ACUTE ARTICULAR RHEUMATISM.

			ells.									(	Cases,
Between	6,000	and	8,000	 	 	 	 	 					4
44	8,000	66	10,000	 		 	 	 					9
44	10,000	66	12,000	 	 	 	 	 ٠.	. ,			 	12
66	12,000	66	14,000	 	 	 		 					14
			16,000										
66	16,000	66	18,000	 		 		 					23

TABLE	XV	B.—Acute	ARTICULAR	RHEUMATISM	(Continued)
TUDLE	4 1 . ,	D. TICUIE	LINITOCHAN	THEOMATION	( Concentiated)

LDEL IL .	, 2.	1100	111 111	LILO	. 432414	Terris	OMATION	(000000	idea).
		hite c							Cases.
Between 1	18,000	and	20,000						8
" 6	22,000	46	24,000						5
" 6	26,000	66	28,000						2
₩ €	30,000	44	32,000						3
"	38,000	66	40,000						1
									119

TABLE XV., C.—SUBACUTE ARTICULAR RHEUMATISM.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	62			20,700	62	First day.
				13,700		Fourth day.
2 3	23			19,500	60	
	33			18,200	85	
4	36			18,200		•
				15,600		Sixth day.
5	32			17,500	70	
6	22		5,040,000	17,200	55	
7	23			16,000	45	
8	31			15,200	72	
9	25	Μ.	4,750,000	15,000	60	
10	68			14,900	55	
11	23			14,900	100	
12	13		4,430,000	14,500		
13	50			14,200	65	May 24th.
				6,800		May 28th; mitral regurgitation.
14	45			13,600		
15	30	F.	4,644,000	13,000	60	
16	15		3,820,000	12,000	50	
17	32			11,400		Temperature 100°.
18	28	F.		10,600		•
19	25			10,500		
20	33			10,500		Temperature 100.5°.
21	17			10,100	65	
22	53			9,900		
23	28		4,684,000	8,000	75	
24	?			7,800	60	
25	Adult.	M.	4,016,000	6,200		
26	Adult.	F.	4,188,000	5,750	73	

# Table XV., D.—Chronic Rheumatism, Chiefly Articular.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	
1 2 3 4 4 5	78 19 32 58 30 20	F. F. M. F. M.	5,248,000 4,744,000 5,576,000 Average =	7,200 8,300 6,400 6,500 6,100 9,800 7,400	2 45 2 60 2 62	

TABLE XV., E.-MUSCULAR RHEUMATISM.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1 2 3 4 5 6 6 7	46 52 54 38 54 27 35	M. M. M. M. F.	4,580,000 4,370,000 4,360,000 3,820,000 ? Average =	7,500 4,006 7,500 6,600 14,000 6,000 5,700 7,328 +	70 55 75 ? 58 ? ?	During febrile attacks. Lumbago.

The average leucocytosis in the acute cases is 16,200; in those mild and more chronic, so-called "subacute" cases the leucocytes range lower, averaging 9,760; while in chronic rheumatism, whether articular or muscular (including lumbago), there is no increase at all (average=7,450). In acute cases the leucocytosis subsides with the joints, rising again if relapse or complication occurs. The polynuclear cells are absolutely increased with an absolute diminution of the lymphocytes. The eosinophiles rarely disappear as in most infections. After the very earliest days (when they may be scanty or rarely absent) they are increased despite the fever and exudation. In convalescence they run even higher, 13.8 per cent (or 970 absolute) in one of Türck's cases. During the fever Türck noted myelocytes and stimulation forms as in other infections.

Blood plates are much increased during the fever.

In 25 cases of arthritis deformans treated at the Massachusetts General Hospital the blood was normal except for a slight deficiency of hæmoglobin in two cases.

# Summary.

Anæmia with leucocytosis, the degree of which is a measure of the severity of the infection. Fibrin much increased.

# Diagnostic Value.

The blood tells us little if anything that could not be learned in other ways. It does not differ at all from that of a septic arthritis, or from that of acute gonorrheal arthritis.

The only cases that I remember in which a blood examination has been valuable are the following:

Case I.—The patient had muscular pains, fever, and a history of a malarial attack some months earlier. The question to be decided by the blood examination was between malaria and "rheu-

matism." The leucocytes were 23,600 per cubic millimetre, which made it clear that the case was neither malaria nor "rheumatism," since the former never increases the leucocytes and the latter could give so high a count only in case genuine articular inflammation were present. The case turned out to be croupous pneumonia

which the high leucocyte count strongly suggested.

Case II.—The patient presented symptoms and signs of acute polyarticular rheumatism with fever. The fever came down under salicylates, but soon rose again, and the man became wildly delirious. His delirium persisted after the salicylate was stopped. Several joints continued swollen and tender. The fever was very moderate, ranging between 99° and 101°. There were no rose spots and no enlarged spleen. The question arose as to whether it was a case of sepsis with localization in the joints, or whether it was a case of typhoid supervening on an arthritis of some kind. The blood count, which was repeated several times, always showed a perfectly normal blood except for a slight anæmia. The subsequent course of the case, during which he remained for nearly three weeks more or less delirious, made it clear to Dr. F. C. Shattuck, under whose care the patient was, that the diagnosis was typhoid.

Chronic rheumatism (muscular or articular) produces no constant blood changes appreciable by clinical methods (see Table XV., D

and E).

### ASIATIC CHOLERA.

In no other disease, so far as I am aware, has an *acid reaction* in the blood been reported. This is at the end of life. All observers agree that the alkalinity is at least greatly reduced.

Our knowledge of the corpuscles is best summed up in Biernacki's study of thirty-eight cases.

Red Cells.—In the stadium algidum, or stage of collapse, most of the symptoms are due to the great concentration of the blood from the loss of serous fluid in the stools. Hayem found the increase of red cells from this concentration to amount to from 1,000,000 to 1,500,000 per cubic millimetre.

Biernacki <sup>1</sup> found 7,662,500 in one case twenty-four hours after the beginning of the disease. The specific gravity may be as high as 1.071 or 1.072.

White Cells.—Leucocytosis is present, not merely as the result of concentration, but as a genuine increase to at least double the normal count. Biernacki found that cases with particularly high counts (40,000 to 60,000) were soon fatal, so that he considers a marked leucocytosis in the algid stage as a bad prognostic sign, al-

<sup>&</sup>lt;sup>1</sup> Deut. med. Woch., 1895, No. 48.

though patients also die with low leucocyte counts in this period. Such a leucocytosis does not occur in ordinary diarrhœa or dysentery.

Leucocytosis is present as early as twelve hours from the first symptom and lasts at least as late as the sixth day. In the stage of reaction it usually decreases. In one very mild case reported by Biernacki there was not only no increase, but leucopenia (4,375 per cubic millimetre).

The differential count shows from eighty-two to ninety-five per cent of adult cells and a corresponding diminution of the young forms.

### ERYSIPELAS.

Ehrlich, Halla, Pée, Reinert, Rieder, and von Limbeck agree that leucocytosis is usually present in well-marked cases. Von Limbeck finds the "leucocyte curve" to run roughly parallel with the temperature chart, sometimes beginning to fall a little before the latter. The counts rarely run very high, yet Reinert counted 39,627 in one case. Pée noted that the leucocyte count increases only while the process is spreading, and that the size of the count was a tolerably accurate measure of the severity of the case.

Rieder found in seven cases an average of only 15,000 per cubic millimetre despite very high temperatures. In one case the leucocyte count remained high after the temperature had fallen, but in the others it anticipated the temperature. In one mild case he found no leucocytosis. Polymorphonuclear cells are greatly increased as in other forms of leucocytosis. Hayem noticed the same dependence of the leucocyte count upon the severity of the process.

Case.	Age.	White cells.	Remarks.
1	. 28	14,400	First day.
		14,450	Second day.
		17,100	Third day.
		17,300	Fourth day; spreading.
		15,400	Temperature 105°.
<sup>2</sup>	. 25	16,600	
3	. 78	17,000	
£ <b></b>	. 29	14,000	
5	. 51	13,000	
<u> </u>	. 17	12,700	
7	. ?	7,250	
3		6,200	

TABLE XVI.—ERYSIPELAS.

In eight cases at the Massachusetts General Hospital I found leucocytosis in all but two, and these two very mild cases. The polynuclears increase and the lymphocytes decrease as in most infections, and the usual abnormal forms (stimulation forms and myelocytes) may be abundant. Türck records five per cent of myelocytes (320 absolute).

When the disease occurred in "scrofulous" cases, Hayem found only 7,000-8,000 leucocytes per cubic millimetre, while in cases with very extensive process and high fever 12,000-20,000 were present. He found also a loss of 500,000-1,000,000 in the count of the red cells, according to the severity of the case. This showed itself particularly just before the fall of the temperature. I have seen no reference by other writers to the condition of the red cells in this affection.

## TONSILLITIS (FOLLICULAR).

Halla,¹ Pick,² and Pée³ found leucocytosis as a rule in uncomplicated follicular tonsillitis; Rieder found it in a case complicated with acute nephritis.

The following table confirms these observations in the main, though in mild cases no leucocytosis was present.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	2			34,400		
				26,900		
		1		26,300	ļ.	
2	7			28,000		
2	23			23,100		December 24th. Follicular.
0	~0			7,600		December 26th.
4	18			21,200	٠.	December 20th.
4			4 000 000		0~	
5	22	F.	4,368,000	19,200	35	
6	22			18,500		
7	21	F.		18,000		
8	24			18,000		Acute follicular.
9	27	M.		18,000		
10	12			17,300		Streptococcus.
11	21	F.		16,800		P
12	20			16,800		Acute follicular.
13	25	F.		16,200		
14	30	F.	4,750,000	16,000	80	Temperature 101°.

TABLE XVII.—TONSILLITIS.

<sup>&</sup>lt;sup>1</sup> Zeitschrift f. Heilkunde, 1883, p. 198.

<sup>&</sup>lt;sup>2</sup> Prag. med. Woch., 1890, p. 303.

<sup>&</sup>lt;sup>3</sup> Pée: Inaug. Dissert., Berlin, 1890, p. 8.

TABLE XVII.—TONSILLITIS (Continued).

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
15	27	M.		15,500	67	Six days; slight.
16	32			15,000		
17	Adult.	F.	4,860,000	14,000		Follicular.
18	30	M.	4,730,000	13,500	76	Convalescent.
19	24	F.	5,000,000	13,500	68	Follicular.
20	Adult.	M.		13,500		
21	24			13,300		
22	36			13,200		Follicular.
23		M.	4,952,000	12,250	94	
24	24	F.	5,816,000	11,900	65	Streptococcus; slight articu-
				ĺ		lar rheumatism.
25		M.	5,000,000	11,800	90	Follicular.
26	19	F.	4,552,000	11,600	52	
27	18	M.	5,150,000	11,500	83	Chronic recurrent, out in two
28	26			11,000		days.
29	23			10,900	68	Follicular.
30	22	F.	5,016,000	9,600		
31	23	F.		7,925	52	Follicular; slight; tempera-
						ture 99° next day.
32	34			7,700		Bronchitis.
33	45	F.		6,800		
34	Adult.		4,200,000	5,800	60	Follicular.
		1				

The blood examination has no diagnostic value so far as I am aware. It is worth knowing that a simple tonsillitis can cause leucocytosis, to the end that if such is discovered on blood examination we need not suppose that some other process is present to account for the increase.

#### GRIPPE.

"Grippe" is a term very loosely used to designate any infection of relatively short course, especially if catarrhal symptoms are present. Seldom is the diagnosis established by satisfactory bacteriological evidence. In all probability, therefore, many of the cases included in the table below are not true "influenza."

The references to the hæmatology of the disease in literature are very scanty. Orion (Archiv. d. Méd. milit., 1890, p. 280) found fibrin increased during the early days of the disease. Rieder (Münch. med. Woch., 1892, XXXIX.) found no leucocytosis in grippe and but little in the "catarrhal pneumonia" following it (Türck).

The following table shows that the leucocytes are normal in about two-thirds of the cases. Sixty-five of the two hundred and

fourteen cases showed leucocytosis, but in several of these some complication was very possibly present. The absence of leucocytosis is of importance in excluding pneumonia and local inflammatory conditions. The leucocyte count does not help us to distinguish the disease from typhoid. In this decision the serum reaction is our mainstay (see below, p. 458). From malaria it may be distinguished by the absence of malarial organisms. In one case after an operation for traumatic epilepsy, the temperature rose to 104°, with a chill, and the question of meningitis was considered. The absence of leucocytosis excluded the meningitis, and the attack turned out to be grippe, which was just then very prevalent.

# TABLE XVIII.—GRIPPE.

```
White cells.
Between 2,000 \text{ and } 3,000 = 2 \text{ cases.}
         3.000
                    4.000 = 5
         4.000 "
                    5,000 = 13
         5,000 "
                    6.000 = 15
         6,000 "
                    7,000 = 37
         7.000 " 8.000 = 16
         8.000 "
                   9.000 = 16
         9.000 " 10.000 = 22
        10.000 " 11.000 = 23
        11,000 " 12,000 = 17
        12.000 " 14.000 = 21
        14.000 " 15.000 = 10
        15,000 " 16,000 = 8
        16.000 " 17.000 = 4
   66
        19,000 "
                   20,000 = 4
        20,000 "
                   21.000 = 1
              Total cases = 214
```

### Red cells.

```
Between 3,000,000 and 4,000,000 = 2 cases.

" 4,000,000 " 5,000,000 = 9 "

" 5,000,000 " 6,000,000 = 14 "

25 cases.
```

### SEPTICÆMIA.

Puerperal septicæmia, infected wounds, septic arthritis, septic endocarditis, general infections with pyogenic bacteria, "pyæmia," are all identical so far as their effects on the blood are concerned, and will be considered together under the general head of Septicæmia.

## Bacteriology of the Blood.

Cocci can be demonstrated in cultures from the blood of septicæmia more frequently than in any other class of infections. Rosenbach in 1884 found streptococci and staphylococci in sepsis.

Garré<sup>2</sup> in 1885 found the last-named coccus in a case of osteomyelitis. In 1890 v. Eiselsberg<sup>3</sup> found staphylococci in ten cases of septic wounds and one case of osteomyelitis, and streptococci and staphylococci together in five more patients whose wounds had become septic.

Czerniewsky, Stern, and Hirschler found the same organisms in puerperal fever, the former observer in five cases.

Brunner, Hoff, and Blum found pyogenic staphylococci in pyæmia and sepsis, and Saenger, Roux and Lannois, Cantu, 11 and Bommers<sup>12</sup> had equal success, each in a single case.

Canon<sup>13</sup> and Sittman<sup>14</sup> investigated large numbers of cases with many positive results, and Grawitz<sup>15</sup> and Petruschky<sup>16</sup> and Cohn<sup>17</sup> were successful in finding pyogenic cocci in the blood of cases of ulcerative endocarditis as well as in other septic infections. Herschlaff 18 found them in erysipelas, acute tuberculosis, perforated typhoid ulcer, etc. Kühnau, 19 on the other hand, was unable to find anything in the blood of twenty-three severe pyæmic cases, and was successful in only one out of twelve cases of ulcerative endocarditis.

Taking the results of all these investigators together, it seems evident that in some cases of septicæmia, blood cultures, taken according to the directions on page 47, show the presence of pyogenic organisms, and that in obscure septic cases the diagnosis may be greatly facilitated by such an examination. Negative results are of course very far from excluding septicæmia, but positive ones are sometimes of great value if proper precautions are taken in the technique of the examination. In the diagnosis of

<sup>&</sup>lt;sup>1</sup> "Microorganismen b. d. Wundinfectionskrankheiten," etc. Wiesbaden, 1884.

<sup>&</sup>lt;sup>2</sup> Fortsch. d. Med., 1885, No. 6.

<sup>&</sup>lt;sup>3</sup> Wien.klin. Woch., 1890, No. 30.

<sup>&</sup>lt;sup>4</sup> Archiv f. Gynäkol., 1888, No. 33.

<sup>&</sup>lt;sup>5</sup> Wien. med. Presse, 1888, No. 28.

<sup>&</sup>lt;sup>6</sup> Wien. klin. Woch., 1891, No. 20.

<sup>&</sup>lt;sup>7</sup> Dissert., Strassburg, 1890.

<sup>&</sup>lt;sup>8</sup> Münch. med. Woch., 1893, No. 16.

<sup>&</sup>lt;sup>9</sup> Deut. med. Woch., 1889, No. 8.

<sup>&</sup>lt;sup>10</sup> Revue de Méd., 1890, No. 12.

<sup>&</sup>lt;sup>11</sup> Rif. Med., 1892, No. 96.

<sup>&</sup>lt;sup>12</sup> Deut. med. Woch., 1893, No. 16.

<sup>&</sup>lt;sup>13</sup> Deut. Zeit. f. Chirurg., 1893, p. 571.

<sup>&</sup>lt;sup>14</sup> Deut. Arch. f. klin. Med., 1894, p. 573.

<sup>&</sup>lt;sup>15</sup> Charité-Annalen, 1804, vol. x.

<sup>&</sup>lt;sup>16</sup> Zeit. f. Hygiene, 1894, pp. 59 and 413.

<sup>&</sup>lt;sup>17</sup> Deut. med. Woch., 1897, No. 9.

<sup>&</sup>lt;sup>18</sup> Sem. Méd., 1897, p. 105.

<sup>&</sup>lt;sup>19</sup> Deut. med. Woch., 1897, No. 25.

malignant endocarditis, often a most difficult one, Grawitz thinks blood cultures are especially important and likely to prove positive when the disease is present (see Diseases of the Heart, p. 316).

Almost all observers agree that the finding of pyogenic cocci (except the staphylococcus albus) in the blood makes the prognosis almost surely fatal. The *toxicity* of the blood is doubled.

Red Cells.—All observers agree that very marked anæmia is present in severe cases. Red marrow post mortem I have seen in two instances. Roscher's investigations tend to show that the diminution in red cells in septicæmia is greater than in any other infective disease, and appears in a shorter time. He found such a diminution present no longer than a few hours from the beginning of the illness. He finds the amount of anæmia proportional to the severity of the case, and (reckoning by means of the estimated solid residue) concludes that whenever the blood has lost one-quarter of its substance or more, death follows. He considers, therefore, that help as to prognosis is given us by the blood examination in septicæmia.

The serum becomes very watery, partaking of the general atrophy of the blood tissue. In a case of intensely acute puerperal sepsis Grawitz found the red cells reduced to 300,000 (!) although the patient had been sick less than twenty-four hours. The case seems almost incredible, but is reported in great detail in the author's recent text-book, to which reference has so frequently been made. He accounts for it by the combination of blood destruction and dilution.

In seventeen cases of puerperal sepsis seen at the Massachusetts General Hospital in recent years the red cells averaged 3,800,000, which is very low, considering the shortness of the illness in most cases. (The influence of hemorrhage during parturition must of course be taken into account.)

In most of the septic wounds which I have seen the counts have not been low. But in one case of septicæmia from a suppurating fibroid of the uterus the red cells numbered only 1,800,000. Ewing reports a septic endometritis with 1,600,000 red cells. In a case of puerperal sepsis of only a few days' duration, in a woman not previous anæmic, Hayem' recently reports the following figures:

<sup>&</sup>lt;sup>1</sup> Inaug. Dissert., Berlin, 1894. 
<sup>2</sup> La Méd. Moderne, January 13th, 1897.

December	6th—Red cells	2,578,000	
	White cells	8,000	
	Hæmoglobin	40	per cent.
December 2	4th—Red cells	4,231,000	
	White cells	7,200	
	Hæmoglobin	65	per cent.
(Recovery.)			

Such cases are the best examples we have of an acute anæmia (hemorrhage excepted).

The hæmoglobin is usually diminished about as much as are the corpuscles. Nucleated red cells are very often seen; whether or not they have prognostic value cannot yet be stated. In differential diagnosis their presence helps us to exclude typhoid and miliary tuberculosis, in which diseases they rarely are found.

Deformities in the shape and size of the corpuscles are not usually marked except in the severest cases. Ewing has noted a reduction in the diameter of the cells in anæmic cases.

TABLE XIX.—PUERPERAL SEPTICÆMIA.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks,
1 2	31	F.	0 000 000	77,500		Autopsy.
3	21 29	F. F.	2,300,000	26,000	68	T 1 1-1:
ð	29	r.	3, 900, 000	23,900		Two days before delivery.
				21,000	• •	Day of delivery.
				9,500	• •	One day after delivery.
				15,500	• •	Five days after delivery; breasts caked.
				15,000		Ten days after delivery.
				11,800		Twenty-six days after delivery.
4	28	F.	3,784,000	22,000	55	Miscarriage five days before; septic; curetted.
				13,600	• •	Three days later, temperature falling.
				8,300		Seven days later, temperature normal.
				15,800		Fourteen days later, temperature up; curetted again.
				14,900		Fifteen days later, temperature falling.
				15,000		Sixteen days later, temperature falling.
				9,500		Thirty-two days later, temperature falling.
5	25	F.		20,800	55	ature fairing.
6	34	F.		15,900		September 2d, 1897.
U	94	F.		35,600	• •	September 2d, 1697. September 9th, chills.
				33,000	• •	September 13th.
				35,600	• •	September 16th. Recovered.
	1	ı		00,000	• •	Beptember 10th. Recovered.

TABLE XIX.—PUERPERAL SEPTICÆMIA (Continued).

No.	Age.	sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
7	25	F.	2,936,000	20,000	50	April 1st, 1894.
				21,000		April 3, 1894.
8	32	F.	4,904,000	19,300		Curetted.
				9.300		One week later, well.
9	24	F.	3,556,000	18,400		
10	, ,	F.		Marked		Polymorphonuclear cells, 94%;
	20	-	~ 000 000	increase.		lymphocytes, 6%.
11	26	F.	5,368,000	5,600	1.2	Died.
12	24		3,428,000	33,500	45	With general peritonitis.
40			0 500 000	28,800		Secondary operation.
13	19		3,536,000	9,600		July 18th. Pelvic cellulitis. Diff.
						count 500 cells (chlorosis).
						Polynuclear, 73%; lympho-
						cytes (s.), 22; lymphocytes
						(l.), 4; eosinophiles, 1%. Reds
						slight irregularity in size and
				0.000		shape. No nucleated reds seen.
- 4	00		4 400 000	6,800	12	July 29th.
14	23		4,400,000	14,500	45	May 2d. With toxic nephritis.
				13,400		May 9th.
				7,400		May 14th.
				17,500		May 24th.
				12,200		May 28th.
15	26		4,056,000	9,300	30	June 3d.
10	20		4,030,000	12,400	90	June 8th. Secondary anæmia. Polynuclear, 86.6%; lympho-
						cytes (s.), 9.4%; lymphocytes
						(l.), 3%; eosinophiles, .8%; my-
						elocytes, .2%. Reds stain
						palely in centres, moderate
						poikilocytosis and irregularity
						in size. Normoblasts, 1.
				14,800		June 14th.
				18,400		June 28th.
16	27			12,200		December 5th.
				8,200		December 9th.
				11,400		December 11th, died. P., 140-
			1	,		170; T., 103°-105°; R., 35-60.
17	40			9,200		T. 104°. Recovered.
			1			

TABLE XX., A.—SEPTIC WOUNDS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin,	Remarks,
1 2 3	37 28 31	F. M. F.	5,880,000 7,600,000 5,680,000	25,400		Sloughing breast; bedsore. Septic wound of foot. Sloughing breast after cancer operation.
4 5	27		5,840,000 4,450,000 5,600,000	23, 200 10, 500 8, 800		One month later; wound clean. Septic hand. Septic finger.

TABLE XX., B.—SEPTICÆMIA WITH ARTHRITIS.

_						
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	8	M.		25,000		Pus in elbow joint; no injury.
	Ü			43,000		Two days after operation, vent not free; opened further.
				24,000		Seven days after operation.
				20,700		Eight days after operation.
				6,700		Sixteen days after, well.
2	21			23,800		T. 101°.
2 3	34	M.		19,000	65	Gonorrhœal pus in knee.
4	59	M.	[4,520,000]	18,500		Pus in shoulder joint; no trauma.
5	28			18,200		T. 99°.
6 7 8 9	22			17,500	72	Gonorrhœa and syphilis.
7	55			17,500		Gonorrhœal.
8	?			17,100		Gonorrheal.
	28			16,500	* *	Gonorrhœal.
10	42			14,100	50	Gonorrheal.
11	22			13,800	::	Gonorrhœal ankle.
12	16			13,300	52	Gonorrheal.
13	32		3,864,000	12,500		T. 99°. Gonorrheal.
14	32			12,200		T. 102°. Gonorrheal.
15	33			11,900		Gonorrheal.
16	32			9,700		T. 101°. Gonorrheal.
17	21			9,400		Gonorrheal.
18	28			9,100		Gonorrheal.
19	28	::		9,000		Gonorrheal.
20	39	М.		8,940		Ankle gonorrheal. Cultures negative.
21	?	:		8,800	76	Gonorrhœal.
22	32			6,200		T. 101°. Gonorrheal.
23	21			6,200		Gonorrhœal.

TABLE XX., C.—GENERAL SEPTICÆMIA.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.			
1 2	Adult.	M. F.	5,248,000 1,800,000	41,400 46,000		Suppurating fibroid. Strepto-			
3	22	F.	3,776,000	25,800	52	A fatal case, yet no fever! Strep-			
			,,,,,,,,,,	100,000	0.0	tococcus.			
4	44			20,700		Cholangitis.			
				30,700		Pus in eye and throat. Strepto-coccus.			
5	43			12,100		Cause?			
6	20			27,000		Septic leg, pus burrowing.			
7	11			10,800		December 15th.			
i				13,000		December 17th.			
				18,600		December 19th.			
				19,400		December 20th.			
				13,200		December 21st.			
i			Į	12,200		December 23d.			

-						
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
		-		12,400		December 26th.
				10,400		December 28th.
				11,000		January 5th.
				22,000		January 15th.
				34,000		January 19th. Autopsy.
8	33			24,000	75	April 24th.
				19,400		April 26th.
				18,000		May 1st.
				19,600		May 3d.
				43,200		May 11th. T. 104\frac{4}{4}^{\circ}. No au-
						topsy.
9	55			10,100		Pneumococci in blood. Autopsy.
10	33		4,160,000	22,000	45	Multiple septic embolism. Sugar
						in urine.
				16,000		Tenth day.
-				22,000		Seventeenth day. Autopsy.
11	38			19,800		First day.
				29,100		Third day.
				27,200		Fourth day.
				25,200		Sixth day.

TABLE XX., C.—GENERAL SEPTICÆMIA (Continued).

Hæmoglobinæmia with reddish staining of the serum is often noticeable in the dried and stained cover-glass specimen when the plasma is deeply stained.

Leucocytes.—Considerable controversy has taken place as to the changes in the white cells effected by septicæmia; some observers finding leucocytosis, while others find none.

The results of experimental infections referred to above (see p. 110) and the parallelism of the leucocyte changes in pneumonia, peritonitis, and diphtheria fully explain these apparent divergences, which perfectly exemplify the rules stated on p. 105.

Leucocytosis occurs only when the struggle between the patient and his disease is intense, and whichever is victorious. When either side wins without any difficulty, *i.e.*, in the mildest and in the severest cases, leucocytosis is nearly or entirely absent; indeed, leucopenia may be found (as for instance in a case of septic endometritis reported by v. Limbeck—only 3,000 leucocytes). Von Limbeck and Krebs¹ found no leucocytosis in cases of puerperal septicæmia, but these were all fatal cases or very mild ones. Rieder, on the other hand, and the great majority of other observers (Sadler,² Roscher,³ Kanthak,⁴ Grawitz, etc.) find leucocytosis. This

<sup>&</sup>lt;sup>1</sup> Krebs: Dissert., Berlin, 1893. <sup>3</sup> Roscher: Dissert., Berlin, 1894.

<sup>&</sup>lt;sup>2</sup> Sadler: Loc. cit. <sup>4</sup> Kanthak: Brit. Med. Journal, June, 1892.

means that in most cases observed by these writers the infection was of moderate severity. Ewing's experience leads him to the conclusion that while the rule that suppuration produces leucocytosis is almost invariable, it must be remembered that leucocytosis may promptly disappear when exudation ceases, and that suppuration involving mucous surfaces may induce very slight leucocytosis.

Only 14 of the 56 cases in Tables XIX. and XX. showed no leucocytosis. One was very mild, the other proved fatal on the day of the count. The leucocytosis is of the ordinary polynuclear type with disappearance of eosinophiles and diminution of lymphocytes. Myelocytes and "stimulation forms" are usually present in small numbers. The reappearance of the eosinophiles seems to me to have some favorable prognostic significance.

## Summary.

- 1. Rapid development of severe anæmia.
- 2. Leucocytosis marked, except in very mild or very severe cases.
  - 3. Blood cultures may contain pyogenic cocci.

# Diagnostic Value.

The advantage of a positive bacteriological examination is obvious. Of the value of the blood count in distinguishing septic from non-septic wounds and estimating the degree of sepsis and the importance or needlessness of operative interference, not much is known. The subject deserves to be carefully worked out from a surgical point of view. The following cases, however, tend to show that we might utilize blood counting far more than we do to determine questions of this sort:

Case I.—Frank B—— suffering with appendicitis was operated on by Dr. M. H. Richardson at the end of an attack. A little pus was found, the appendix was excised, and the wound nearly closed, a small strand of gauze, however, being left in. Several days after the operation, there being at the time no external discharge, the temperature rose. The wound seemed perfectly clean. The man was very nervous about himself, and much stirred up at each dressing; and as the temperature never went higher than 101°, there seemed to be considerable doubt as to what the cause of the elevated temperature was. The blood count in this case showed 52,000 leucocytes. On opening the wound a large amount of broken-down blood clot was evacuated, and the temperature came down to normal.

Case II.—Mrs. S—— had a pust ube shelled out and the abdominal wall was sewed up tight. Ten days after the operation the temperature began to look as if pus were present. Here again the patient was exceedingly nervous; and, as so often happens, the question was asked and re-asked, whether she was keeping up her own temperature by the state of her mind. The blood count, however, showed marked leucocytosis, which led to a careful ether examination, revealing a fluctuating mass behind the uterus, from

which pus was obtained by puncture.

Case III.—Mr. R—— entered the Massachusetts General Hospital in December, under the service of Dr. C. B. Porter, with a compound fracture of the thigh. Some days after it had been put up, the temperature began to suggest the presence of pus, the wound, however, remaining perfectly clean. I counted the blood, and found a marked leucocytosis. A more thorough exploration of the wound revealed a pocket of pus, the evacuation of which brought down the temperature. I was not sure in this case whether the absorption of the blood clot, such as takes place, I suppose, after any compound fracture, would be sufficient to cause leucocytosis. I therefore counted several cases in which there was fever and presumably blood-clot absorption, namely, a hæmothorax, a pelvic hæmatocele, two compound fractures, and a crushed foot; in none of these was any leucocytosis present.

Case IV.—Mr. S— was operated on by Dr. J. C. Warren for traumatic epilepsy. Nothing special was found, and the wound was closed. Ten days after the operation the temperature rose to 104°, and the patient complained of severe headache and pain in the back. I counted the blood, and found no leucocytosis. Next day the temperature was down. The patient apparently had the

grippe.

Several cases in which an old malaria was supposed to be "brought out" by a surgical operation, the patient having irregular fever and chills after the operation, have shown, on examination of the blood by the writer, no malarial organisms but marked leucocytosis. In these cases the symptoms of "malaria" ceased when the wound was more thoroughly drained, and I have no doubt that many cases of "malaria" after surgical operations are really wound sepsis.

It is difficult to make inferences from a leucocytosis in such cases, because no one, so far as I know, has thoroughly investigated the blood condition during the normal healing process of wounds. But there are certainly many cases in which we need the kind of information about the condition of a wound which the blood might give us, if the changes in connection with wounds were better known.

How often the questions are asked: Is this patient septic? Does this temperature mean anything of importance? Is this wound well drained? Is this complaint of pain hysterical or does it mean something operable?

ABSCESS.

How often the blood count would help us to answer such questions without leaving it for time to settle them after the most urgent need of settling them is gone, we do not yet know.

In puerperal cases, the fact that leucocytosis is always present for several days after delivery makes it harder to judge from the blood whether a given case is septic. I doubt if the blood count will give any information on this point not to be more easily obtained in other ways. Blood cultures, if positive, are of far greater importance, but take more time.

### ABSCESS.

# Iodophilia.

Goldberger and Weiss' have recently applied the iodine reaction originally described by Ehrlich and Gabritschowsky to the study of the polynuclear leucocytes of the blood in cases of *local suppuration*. A syrupy mixture of the following elements is made:

Iodi sublim	1
Pot. iodidi	3
Aq. dest	100
Acacia ad syrunum	

This is painted on a slide and the unstained cover-glass preparation is pressed down into it. So treated normal blood or that of non-suppurative diseases shows the following: red cells dark yellow; white cells light *yellow* with very refractile, citron yellow nuclei.

In purulent affections the protoplasm of the leucocytes stains brown, either diffusely or in a granular or network distribution.

Kammier<sup>2</sup> distinguishes three stages in the appearance of the reaction:

- (a) A slight diffuse brownish discoloration of the protoplasm.
- (b) A concentration of the brown color into intensely stained flakes and granules. (This is the type most often seen.)
  - (c) An intense brown discoloration of the whole protoplasm.

Czerny, and recently Hofbauer, have found iodophilia in cases of grave anæmia, primary or secondary. In chlorosis and the

<sup>&</sup>lt;sup>1</sup> Wien. klin. Woch., 1897, No. 25.

<sup>&</sup>lt;sup>2</sup> Deut. med. Woch., April 3d, 1899.

milder types of secondary anæmia it is not present unless there is pus somewhere in the system. Leucæmia usually shows a positive iodine reaction both in the polynuclear leucocytes and in extracellular flakes. Hodgkin's disease, on the other hand, shows no such reaction. In purpura, contusions, and hæmatoma, the extracellular flakes reacting to iodine are abundant.

After an abscess is opened the brown color is at first confined to the periphery of the cell and soon disappears altogether. "Cold" abscesses, no matter how large, do not produce the reaction, but acute felons with only a thimbleful of pus have shown marked iodine reaction.

Leucocytosis due to non-infective agents (e.g., spermin) is not associated with any such reaction. On the other hand, it is not peculiar to infections which produce pus. In pneumonia, in puerperal sepsis without localization, and in non-suppurative terminal infections a well-marked iodophilia may occur.

It has also been found in cases of fracture and after severe contusions or prolonged narcosis.

## Other Effect of Abscess on the Blood.

The effects of abscess upon the blood are, I suppose, due to septicæmia. Nevertheless septicæmia with abscess formation differs enough from septicæmia without abscess formation, both clinically and hæmatologically, to make a separate description convenient.

The most easily studied variety of abscess is that connected with appendicitis, inasmuch as the frequency of operations in such cases gives us opportunity to verify what we suppose to be indicated by the blood count and see how far our suppositions are true.

At the Massachusetts General Hospital, most patients with other varieties of abscess go straight to the surgeon and their blood is not examined, but many cases of appendicitis come first to the medical wards, and hence we have records of over eighty cases whose blood has been examined.

I shall therefore begin the description of the blood in abscess by an account of appendicitis, which may probably be considered a typical case of abscess formation.

### APPENDICITIS.

After excluding all cases in which the diagnosis was not sure we have left seventy-two cases.

TABLE XXI.—APPENDICITIS.

-	_					
	9.	,,	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
No.	Age.	Sex.		S 0	Pe pg	
1 2 3	43 40	M. M.	3,400,000 6,800,000	52,000 43,000		Question of typhoid; pus found at operation, Chronic case; 96 per cent. of adult leucocytes.
3 4	30	F.	5,184,000	39,900 36,800		·
5 6	50		4,800,000 4,290,000	36,000 35,000		
7 8 9	?	 М.	6,000,000 6,500,000 5,072,000	34,000 34,000 28,000		Three days after operation. Seven " " "
10		111.	3,012,000	24,200		Second attack; operation at 11 p.m. November 5th, count at 5:30.
				16,850 15,600	•••	Serous peritonitis found. November 6th, 5 p.m. November 7th, 3 p.m.
				10,700		" 8th, 4 "
				15,100		Temperature still up. November 9th, 5 p.m.
				14,600 11,800		November 10th, 5:30 P.M.
				17,850		" 11th, 8:30 " 12th, 8:30 "
				18,200		" 13th, 8 A. M.
				13,100		" 13th, 8 A.M. " 13th, 8:30 P.M.
11				24,000		Recovery complete ten days later. 24° September 1st; operation, free turbid fluid without
				12,500		adhesions. September 10th.
				19,500 24,000		" 12th; pocket of pus found.
12	23	M.	5,200,000	24,000	00	
13	•••	• • • •	5,144,000	23,000 16,100	82	January 14th.
14		M.		22,500		" 15th; before operation, $\S v. + pus.$ Not operated; entrance.
				13,000		Second day,
				9,500		Third "
15	• •	M.		22,300 9,500		12:20 operated; belly full of pus. 8:30 moribund; blood dark and hard to get.
16	35	F.		22,000		July 6th.
				19,400		" 8th.
nd 194		2.5		14,900		" 10th, T. 104°; recovery.
17	• •	M.	*****	21,900		Appendicitis eight to nine days; operation; post-cæcal abscess.
18				21,700		November 5th, first operation.
				21,400		" 10th.
				16,000		" 13th.
				24,400		" 15th. " 16th.
				47.700		" 19th, second operation (pus pocket).
				20,200 47,700 16,700		" 20th.
				13,000		" 21st.
				10,700 30,300		" 22d,
				20,900		" 26th, third operation (pus pocket). " 27th,
				17,700		" 28th.
				25,100		" 29th.
				28,100		" 30th.
				20,400 15,400		December 1st. 2d.
				25,000		" 3d.
				11,900		" 4th.
				15,600		" 5th.
				21,900 19,000		" 6th. " 7th.
				11,900		" 8th.
				12,800		" 9th.
				11,700		" 10th.
				12,300 15,600		" 11th. " 12th.
				13,400		" 13th.
				13,400 14,700		" 21st.
				16,500 11,300		" 25th.
19	31	M.		11,300		2011
20	01	ATA.	10	20,540		October 5th.

TABLE XXI.—APPENDICITIS (Continued).

=	_					
				Q.	n - int	
	1		Red.	White cells.	Per cent hæmo- globin.	Remarks.
No.	ge	Sex.	88 99	ce ₹	Per Per	
Z	Age.	ŭ			_ a	
-	31	M.		33,000		October 6th.
30	. 01	101.		14,640		" 8th.
				9,200		" 9th; moved bowels.
	1			21,000		12th; tender still and tense.
				24,900 13,700		99° to 100° temperature. Normal: still sore.
20		M.		10,100		Appendicitis twenty-four hours; resistant belly.
-				20,100		Appendicitis twenty-four hours; resistant belly. October 23d.  24th, 9 A.M. 24th, 4 P.M.
				14,000		" 24th, 9 а.м.
	1			12,400		
	1			13,250 8,750		" 25th 8 A M : liquids every two hours.
				9,600		" 25th, 3 P.M.
21	24	F.		20,000		May 24th. " 25th.
90				19,000 20,000		Tuno 5th temporature 101 40; pain and remiting
42				9,000		June 5th; temperature, 101.4°; pain and vomiting.
	i			10,000		June 7th; no pain.  "8th; no pain; temperature, 100.6°; discharged.
23			4,800,000	20,000		Operated; pus.
24	1		5,564,000 4,670,000	20,000 19,750		January 19th
20		• • • •	5,296,000	15,000		January 13th.
26	20	F.		19,600		" 29th,
			4,680,000	12,000		February 1st.
27			4,688,000	8,933		" 5th; after operation.
21	58	М. М. М.	5,120,000	19,500 19,000		No operation. Purulent peritonitis.
29	30	M.	5,680,000	18,930		l di dicat portonios
30	14	M.		18,000 17,500		
31		M.		17,500 16,250		Accident case; operation; pint of pus under pressure. Fifth day. November 7th.
94	20	24.	******	17,450		November 8th.
			1	12,000		" 11th; not operated; well on 17th.
		M.		16,200		
34	10	F.		16,200 16,051		Eighth day; operation; large abscess cavity.
36	40	F.		16,000		Operated. Entrance.
00	1			8,000		Same evening; no operation.
				7,500		Next day.
2~			6,160,000	6,800 16,000		General peritonitis,
38			0,100,000	16,000		November 12th, noon,
				8,000		" 12th. 8: 30 p. m.
				7,500		" 13th, 8 A.M.; not operated.
20	1		3,300.000	6.600		" 13th, 8 р.м.
40	17	М.	4,380,000	16,000 15,600	66	March 25th, 9 p.m.; vomiting, pain, tenderness.
	1	-	_,,,,,,,,,,	19,500		" 27th; comfortable, no vomiting; signs more
				22.000		localized.
				22,900		" 28th; slight tenderness only. " 29th; bowels move well; no symptoms.
	1			35,300 32,800		" 30th; operation; large amount of pus.
41	27	M.	4,330,000	15,523		,
42	23	M.	5,910,000	15,330		2041
43	22	M.		14,800		20th; general peritonitis. 21st; ""
44				14, 700		Five days; third attack; operation; free turbid fluid,
			1			no perforation; prompt recovery.
45	36	F.	4,250,000	14,700	70	27th, 8 p.m.
46	92	F.		13,150 14,400		February 23d /
70	1	1.		10,300	1	28th; symptoms less; no operation. February 23d. ( 3 ij. foul pus.
47	١		4,950,000	14,000		Catarrhal.
48				13,400		3 P.M., November 9th: appendicitis twenty-four nours.
40	1		5,000,000	11,200 13,000		5 p.m., November 10th; temperature, 98.8°.
50			3,000,000			Visible tumor. March 27th.
	1			17,000		" April 26th, operated; pus.
51	1		4,626,000	12,000	1	

TABLE XXI.—APPENDICITIS (Continued).

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
52		M.		12,000		Appendicitis cake. August 3d, operation; gangrenous appendix with adhesions.
<b>5</b> 3		M.		16,900 11,900		August 6th, fæcal fistula. No symptoms except pain for twenty-four hours; not operated.
54	51	М.		11,800		Very slight tenderness; no resistance or dulness, July 6th.
<b>5</b> 5		М.	4,860,000	19,900 11,700 17,600 16,670 11,950 10,800	58	Temperature up; tenderness and resistance. July 7th, operation; pus found. December 28th, 4 P.M. " 30th, 10 A.M. " 31st, 11 " January 1st, 9 P.M. " 5th.
<b>5</b> 6	22	F.	4,664,000	10,875 21,000		July 27th; nine days pain and vomiting. July 28th; more pain, tenderness and vomiting; opera- tion showed pus.
57		M.		10 700 9,000 10,500		November 7th, appendicitis six days. Operation; abscess with considerable pus; gangrenous perforated appendix with concretion in it. Not operated till later.
		F. M.	3,690,000	10,400 9,800 10,400		February 6th, 12 m.; slight pain and tenderness.  " 7th, 3 P.m.; temperature dropping.  Catarrhal.
<b>6</b> 0			5,600,000	10,500		One week, fourth attack; no cake, no acute symptoms;
61		M.		10,040		operation; no pus. Sixth day, operation; abscess, \( \frac{3}{2} \) i. pus.
62 63 64	24	M. M. F.		9,000 8,400 10,000 7,200 7,600		Operated; no pus; catarrhal. December 1st.  6th.  15th.  16th.
		M. M. M. F.	5,106,000 5,600,000 6,500,000 6,500,000 6,000,000 4,320,000	7,760 7,600 7,600 7,630 7,050 7,000 6,600 6,000	85	No pus.  No operation.  No pus.  Catarrhal appendix; five days in hospital.  Catarrhal appendix.  "chronic; nearly well; operation; no pus.  "or very slight.

From the seventy-two cases of the adjoining table, together with ninety-four other counts not here recorded, the following conclusions are to be drawn:

- 1. Red cells: no changes except in chronic cases with long-standing abscess.
- 2. Coagulation often slow, but fibrin always increased in suppurating cases.
- 3. As in most infections the mildest and the severest cases show no leucocytosis. Six cases with general purulent peritonitis showed no leucocytosis, its absence being confirmed by repeated examinations. The total absence of leucocytosis in a case not obviously mild is a very bad prognostic sign as in pneumonia and diphtheria.

- 4. Catarrhal appendicitis is rarely accompanied by leucocytosis (only once in this series—14,000).
- 5. An increasing leucocytosis means a spreading process and may be the only evidence of the fact. In Case 40 of this series, the patient entered with vomiting, localized pain and tenderness. The leucocytosis was 15,600. Three days later he was comfortable, had no vomiting and very little tenderness, and in all respects seemed to be improving, yet the white cells had risen to 22,900. Operation was postponed owing to the lack of all unfavorable symptoms except the blood count. Next day the bowels were moving well and the patient had no fever and no bad symptoms of any kind, but his leucocytes had risen to 35,300. On the following morning the surgeon was finally persuaded to operate and found a large amount of pus.

A steadily increasing leucocytosis is always a bad sign and should never be disregarded even when (as in this case) other bad symptoms are absent. It is of far more significance than a larger count which does not increase.

- 6. The size of the leucocytosis is of comparatively little significance. A low count (8,000–11,000) means one of three things:
  - (a) A mild case.
  - (b) A very severe case.
  - (c) An abscess thoroughly walled off.

After the abscess has ceased to spread and has become well walled off, the leucocyte count remains stationary or decreases. If it bursts into the general peritoneal cavity the count may rise sharply or it may fall to normal or subnormal, its movement depending on the degree of resistance which the system offers.

7. In the majority of cases the pus is neither completely walled off nor free in the belly, and such cases are accompanied by a moderate and fluctuating leucocytosis, which rises and falls according to a variety of conditions which cannot be accurately interpreted.

It usually increases in the first three or four days of the illness, and then becomes stationary or declines if the case is taking a favorable course (i.e., if the pus is being absorbed or walled off), while it continues to increase when the case is going on from bad to worse.

Case 20 illustrates the course of the leucocytes in a favorable case not operated on; the leucocytes fell gradually but steadily from hour to hour so that in two days the count came down from 20,100 to 8,750, the tumor and tenderness simultaneously disappeared, and

the patient was well in a few days more. Case 38 dropped in eight hours from 16,000 to 8,000 and quickly recovered. In Case 19, the leucocytosis fell in three days from 33,000 to 9,200, but rose again when the bowels were moved by enema, and took some days to reach normal again. Evidently the peristalsis injured the abscess wall so that the process began to spread again and had to be walled off afresh.

- 8. When a leucocytosis of 18,000–25,000 is maintained for a number of days it usually means a large abscess pretty well walled off.
- 9. The majority of cases as seen at the Massachusetts General Hospital on the second, third, and fourth days of the illness showed leucocytosis of 15,000–24,000, thirty-three of the present series falling within these figures. Counts larger than this have always been proved to mean a large amount of pus or a general peritonitis. Of the cases below 15,000 (fifteen in all) twelve did not come to operation, or if operated showed no pus. This statement excludes the four cases of general purulent peritonitis without leucocytosis mentioned above.
- 10. Case 18 illustrates several points. After the first operation the leucocyte count did not fall so rapidly as usual, and the cause of this soon turned out to be a pus pocket, after the evacuation of which the count fell in twenty-four hours from 47,700 to 16,700, only to rise again for another accumulation of the same kind.

After this last (third) operation the case progressed slowly but favorably, and yet the leucocyte count remained more or less above normal for a month. The wound was healthy, freely discharging, and had healed satisfactorily at the time of the last count recorded.

Hubbard, in a study of the counts recorded in the surgical wards of the Massachusetts General Hospital, concludes that while the leucocyte count may be of value in distinguishing appendicitis from other non-suppurative affections, it is of little value (when the diagnosis of appendicitis is established) in helping us to predict the further course of the case, or in guiding our judgment regarding the time to operate.

Bloodgood's' results may be thus summarized:

- 1. Chronic cases: leucocytes subnormal with few exceptions.
- 2. Acute cases at end of an attack: leucocytes, 10,000 to 15,000.
- 3. Early acute cases: leucocytes, 8,000 to 22,000.

<sup>&</sup>lt;sup>1</sup> Medical Record, October 20th, 1900.

- 4. Gangrenous appendicitis: leucocytes, 13,000 to 25,000.
- 5. Appendix full of pus: leucocytes, 15,000 to 35,000.
- 6. Appendix with abscess: leucocytes, 6,000 to 60,000.
- 7. In acute cases, if operation is delayed, the leucocytes rise with an increase of other symptoms. A rising leucocyte count is a symptom of danger.
- 8. In cases giving a history of appendicitis and a high leucocytosis, but without local signs, one may feel reasonably sure that a deep abscess exists.
- 9. With a leucocyte count of over 20,000 no time should be lost before operating.

# Differential Diagnosis.

1. The presence of a marked leucocytosis excludes simple *colic* with or without constipation, and excludes certain forms of intestinal obstruction (if uncomplicated). Such cases of intestinal obstruction as are complicated with ulceration or gangrene or due to cancer may raise the leucocyte count.

Between general peritonitis from an appendicitis and intestinal obstruction, the presence of marked leucocytosis points to the former; but its absence may accompany either affection. I remember a case in which the diagnosis lay between these two affections, and operation was delayed because the absence of any leucocytosis was thought to rule out peritonitis, and it was hoped to get the bowels started by enemata, etc. When finally the abdomen was opened stinking pus gushed out and the patient died the same day.

- 2. Treves' has reported several cases in which it was hard to decide whether the diagnosis was typhoid or appendicitis. A blood examination would probably have decided the matter, as it has in three cases in the writer's experience. Most cases of appendicitis of any severity show leucocytosis; typhoid almost never does if uncomplicated. Curtis² reports a case of typhoid with a tumor and tenderness in the right iliac region which closely simulated appendicitis but turned out to be a floating kidney. The blood count would have decided the matter.
- 3. Between appendicitis and pus tube the blood gives no help, as both affect it alike.
  - 4. Ovarian or pelvic neuralgia (uncomplicated) never causes leu-

<sup>&</sup>lt;sup>1</sup> Medico-Chirurgical Transactions, 1888, lxxi., p. 165.

<sup>&</sup>lt;sup>2</sup> "Twentieth Century Practice of Medicine," vol. viii., p. 461.

cocytosis and may be excluded by its presence. The same is true of floating kidney, which has been sometimes confounded with appendicitis.

- 5. Gall-stone colic, and renal colic if uncomplicated by inflammatory disturbance, cause no leucocytosis, and can therefore be distinguished from appendicitis in most cases. If cholangitis, cholecystitis, pyelitis, or severe cystitis complicate the colic, the examination of the blood will be no help to us.
- 6. Impaction of fæces in the cæcum will not cause any leucocytosis and may be excluded when such is present. The count may be of use, it seems to me, in deciding us whether an enema ought to be given. It is sometimes desirable to give an enema in cases simulating appendicitis, to help clear up the diagnosis, but some physicians are afraid to do so for fear of causing a walled-off abscess to break into the general peritoneal cavity. In such cases, if no leucocytosis were present, we might go ahead with a clearer conscience.
- Mr. B—— entered the Massachusetts General Hospital September 20th, 1893, with a diagnosis of appendicitis. For twenty days he had been having pain and tenderness in the region of the appendix, pain being controlled by morphine. The bowels had been loose, he said. There were dulness, tenderness, and a distinct tumor in the region of the appendix, with slight pyrexia. The blood count showed only 8,000 leucocytes. He was given a compound cathartic pill, had a large movement of the bowels, and all symptoms and signs disappeared.
- 7. Extra-uterine pregnancy and pelvic hæmatocele may cause leucocytosis like appendicitis, but do not increase fibrin unless peritonitis is present, and are likely to show a marked diminution in red corpuscles if the hemorrhage is severe. The red cells are normal in appendicitis except in chronic cases with abscess.
- 8. Floating kidney has been already mentioned in Curtis' case, in which in combination with typhoid it closely resembled appendicitis. Even without the presence of typhoid, the same difficulty of diagnosis may arise between appendix and floating kidney. The presence of leucocytosis could not be accounted for by the latter.

One of the next most common forms of abscess seen in medical wards is pyosalpinx, which I shall call by the English name of "pus tube." As this produces the same effect on the blood as pelvic abscess or pelvic peritonitis, I shall consider the three processes together.

# PUS TUBE, PELVIC ABSCESS, AND PELVIC PERITONITIS.

Almost all that has been said of appendicitis applies equally well to these conditions.

TABLE XXII., A.—PUS TUBE AND PELVIC ABSCESS.

~~~					
No.	Age.	Sex.	Red cells.	White cells.  Per cent hæmo-	Remarks.
1	36	F.		43,000	Double pus tube; too weak to operate. December 15th.
2	38	F. F.	5,400,000	31,000 45,900 20,200 15,200 12,200 34,000 34,000 34,600 35,000 40,000	December 22d. December 29th; abscess burst per vaginam. January 4th, abscess opened in groin.  "8th. "11th. Pelvic abscess. Pus tube. June 18th. June 19th. "20th. "27th, fever and vomiting just before catamenia.
5678	34 23 29 20 26	F. F. F. F. F.	4,202,000 4,880,000 4,544,000 3,800,000	17,300 11,500 12,000 32,500 30,000 29,200 28,800 27,300 27,000 65	July 1st, temperature normal.  "8th, mass decreasing. "14th, slight thickening still. Pus tube; septic arthritis; jaundice. Pus tube.  Double pus tube. General purulent peritonitis. Pus tubes. Double pus tube. November 17th.
11 12 13 14 15 16 17 18	24 45  35	F.F.F.F.F.F.F.F.F.F.F.F.F.F.F.F.F.F.F.	5,210,000 5,120,000 5,376,000 3,760,000 5,200,000 5,200,000 3,704,000	26,600 24,400 24,400 24,000 23,000 22,000 22,000 21,100 65	Pus tubes. Pus tube. Pus tube. Pus tube. Pus tube. Pus tube. Pelvic abscess (fetid pus). Pus tube. Pus tube. Pus tube. Pus tube. Pus tube; operation; pus found. Pus tube operated.
20 21	26	F. F. F.	5,021,000 4,400,000	16,000 18,600 19,600 21,600 18,200	" "Ith, mass the same; pus tube. Pus tube. Pus tube. Pus tube. Pus tube. No fever. May 4th. " 9th. No fever. May 18th, flow of pus from os started by manipulation.
23	54	F.	3,940,000	19,000 60	
25 26 27 29 29 30 31 33	35	F. F. F. F. F. F.	3,860,000 4,592,000 3,840,000 5,776,000 5,000,000 3,410,000 5,088,000 5,184,000 4,300,000 8,800,000	18,500 55 18,000 18.000 18.000 16,400 18.000 16,000 16,000 15,600 15,600 18,200	Pus tubes.  "tube, "tube, three hours after food.  "tubes, "tube.  "tube, "tube
	36	F.	4,656,000	15.600 60	

TABLE	XXII.—Pus	TUBE	AND	Pelvic	ABSCESS	(Continued).
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No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
36	36	F.	3,696,000	14,975	48	Pus-tube. July 21st, chills and delirium.
			' '	12,600		July 23d.
						" 25th; operated.
37	20	F.	4,310,000	14,800	30	Pus tube; chlorosis.
38	38	F.	3,008,000	13,853	22	Pus tube.
39		F.	4,700,000	12,500	70	Pus tube (double); operated.
40	35	F.		12,200		Pus tube; slight.
41	21	F.		12,200	**, ****	Pus tube. June 2d.
40	19	F.	3,910,000	12,300 12,000		June 10th. Pus tube.
	19		4,756,000	11,850	63	Pus tube. January 5th and 6th.
. 40		r.	4,100,000	13,750	00	i us tube. Sanuary Stil and oth,
44	33	F.	4,240,009	11,000	55	Pus tube. Not operated; very slight.
	47	F.		10,600		Chronic salpingitis. June 21st.
				11,000		June 25th, better.
				11,500		" 29th.
	21	F.	3,800,000	10.400	64	Pelvic peritonitis.
47			7,000,000	10,000		Pelvic abscess (?).
48	38	F.	4,125,000	10,000	60	Pelvic abscess. August 28th.
	l			17,000		September 3d, temperature up.
40	04	771		13,400	• • • • • • • •	" 6th, normal temperature.
49	24	F.		9,000		Salpingitis, 9 A.M.; T. 99.4°.
50	23	F.	472,000	9,200 7,500		4:15 P.M.; five days in hospital. Pus tubes (small; size of finger).
51		F.	5,840,000	7,200		Pus tubes (sman; size of finger).
01		r.	0,040,000	1,200		Lus tube.

From these data together with two hundred and nineteen other counts not here recorded I conclude that: Increasing counts of leucocytes usually point to the need of an operation; stationary leucocytosis to a well walled-off abscess. The size of the count is a rough measure of the size of the abscess, and patients without leucocytosis rarely need operation and usually recover under palliative treatment, as also do many with leucocytosis.

# Differential Diagnosis.

Pelvic pain and soreness may be as great in various non-suppurative conditions (ovarian neuralgia, etc.) as when abscess is present, but the leucocyte count is raised in none of the pelvic disorders of women except abscess, septicæmia (puerperal, after abortion, etc.), and hemorrhage (menorrhagia, metrorrhagia, ruptured tubal pregnancy). Endometritis and cystitis usually cause no leucocytosis. The application of these rules will not infrequently help in the diagnosis of pelvic disease and in deciding how much importance to attach to the complaints of pain, tenderness, etc., in a doubtful case. The absence of leucocytosis makes us rightly confident that no abscess of any considerable size exists.

## OTITIS MEDIA.

Most cases, if purulent, show leucocytosis both before and after paracentesis. If serous (see Table XXIII., cases 7, 14, 15, 17, 18, 19) the count is usually lower, and we can predict with moderate certainty whether serum or pus will be found on puncturing the drum. When the mastoid is involved the count runs higher. If the case drags on, the hæmoglobin may get low, otherwise the red cells are not affected.

TABLE XXIII.—OTITIS MEDIA.

-						
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	6	F.		36,700		Nephritis acuta. April 30th.
				27,300		May 7th.
				34,400		May 14th, otitis only.
				27,000		May 22d.
		7.5		21,000	1::	May 28th, slight discharge still.
2	2	M.		23,000	55	771 . 7 . 77 . 100 . 00
3	19			21,900		Ninth, T. 103.6°.
				13,200		Eleventh, T. 101°.
	0	3.5		10,800	000	Fourteenth, T. 99°.
$\frac{4}{5}$	6	M.	• • • • • • •	18,600	20	337*43
Э	20			17,000	• •	With jugular thrombosis.
	4 =	3.5		21,900	• •	Third day.
6	45	M.	4 700 000	14,500		With cerebral abscess.
7 8	Adult.	M.	4,786,000		65	Serous.
		F.	4,168,000	16,600		Double purulent; vent not free; mastoid sore.
9	19	F.	5,120,000	16,480	88	April 28th.
				8,800	49	May 5th, well.
10	27			15,800		
11	Adult.	F.	5,942,000	15,200		Pus.
12	66	F.	4,472,000	14,750	60	December 7th, hysteria.
			5,416,000	9,750	46	December 25th (during dyspnæic and cyanotic attack).
13	9			13,900		,
14	32			12,000		Serous.
15	24		4,472,000	11,200	20	Serous.
16	22			11,000		
17	27	F.	4,850,000	8,500	69	Serous.
18	7	F.	4,416,000	6,400		Catarrhal.
19	Adult.	F.	4,100,000			Serous.
20	4	Μ.		Marked		Purulent; chronic right, acute
				leuco-		left. Diff. 116 cells; polymor-
				cytosis.		phonuclear cells, 57%; lymphocytes, 31; eosinophiles, 3.

In some cases the blood alone enables us to distinguish otitis and its effects from typhoid. In a case recently examined which several excellent clinicians pronounced typhoid, though there was a marked leucocytosis and no serum reaction, the autopsy showed pus in the jugular and lateral sinus but no typhoid.

### OSTEOMYELITIS.

In four cases in which no external opening was present, the patient complaining only of pain in the bone, the counts of leucocytes were 29,600, 25,600, 24,310, and 18,000; in each the prediction that pus would be found was verified at operation. Three differential counts in chronic cases with sinuses showed nothing remarkable, no increase of eosinophiles and no myelocytes.

The diagnostic value of the blood in osteomyelitis seems to me considerable, inasmuch as it is difficult by the symptoms alone to feel sure enough of the existence of pus to be willing to operate. "Rheumatic pains," "growing pains," and neuralgia can be excluded by the presence of leucocytosis.

## OTHER ABSCESSES.

- (1) Felon.—It is striking to see how small a collection of pus can raise the leucocyte count. Patients with felons containing less than one-half drachm of pus may have a leucocytosis of 15,000 to 22,000. I have counted the blood in three such cases. The element of septicæmia must be considerable. It seems to make no difference whether or not the pus is under great tension. The leucocyte count does not fall sharply after the felon is opened, but gradually diminishes during the next seven to ten days. Even a
  - (2) Gum boil raised the white cells to 27,000 in one case. An
- (3) Abscess of the vulva showed 23,500 leucocytes per cubic millimetre, and an
  - (4) Abscess of the vagina, 12,800. Other varieties are:
  - (5) Parotid abscess, 45,500 leucocytes per cubic millimetre.
  - (6) Subpectoral abscess, 16,000 leucocytes per cubic millimetre.
- (7) Abscess of the neck, 22,200 leucocytes per cubic millimetre. Carbuncle, 41,000 leucocytes per cubic millimetre.
- (8) Psoas abscess (infected), 50,000 leucocytes per cubic millimetre.
  - (9) Abscess of ovary, 26,000 leucocytes per cubic millimetre.
- (10) One case of *perinephritic abscess* was watched for some days while the patient was getting up strength for an operation. It was

an abscess of several months' standing, not increasing in size during the last month, and the counts, as we should expect, did not rise or fall considerably but showed a steady well-marked leucocytosis.

```
July 29th, white cells, 21,400
    " 30th, " " 21,200

August 8th, " " 22,400
    " 11th, " " 23,000
    " 24th, " " 22,200. (Operation.)
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A second case counted showed only 16,000. Both abscesses contained over a quart of pus.

A third case, evidently tuberculous in origin and probably not much infected with pyogenic cocci, showed only 10,000 white cells per cubic millimetre.

- (11) Abscess of the Lung.—Five cases following pneumonia have occurred at the Massachusetts General Hospital within the last three years; the counts were as follows: Case I., 16,800; Case II., 16,000; Case III., 16,400; Case IV., 30,000; Case V., 5,100.
  - (12) Subphrenic abscess, four cases.

Case.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1 2	4,450,000	53, 267 25, 600 15, 500 17, 600	55	May 16th. May 17th. May 20th.
3 4	3,200,000	22,000 15,300 13,800		October 20th. Supposed typhoid for first week. October 23d.
		16,600 18,000 22,500		October 27th. November 5th. November 10th. Operation; a quart of pus; recovery.

# Diagnostic Value.

- 1. The patient with vulvar abscess was so morbidly modest that she complained of all parts of her body except the one diseased, and gave a train of symptoms which failed to account for the leucocytosis. The presence of this leucocytosis called for a much more searching physical examination than would have otherwise been made, and the seat of real trouble was discovered.
  - 2. (a) The diagnosis between perinephritic abscess and cyst of

the kidney is materially assisted by the fact that the former causes leucocytosis, while the latter (see page 335) does not.

- (b) Both cancer of the kidney and perinephritic abscess cause leucocytosis, but if fibrin is not increased cancer is the more likely of the two. This differential mark has served me well in two cases.
- (c) Hydatid of the kidney and pyonephrosis are not to be distinguished from perinephritic abscess by the blood examination. In abscess of the lung the blood gives no information that cannot be more easily gained in other ways.
- 3. Subphrenic abscess may be confounded with malignant disease, both of which may cause leucocytosis; but the absence of any increase of fibrin speaks against the existence of an abscess.

### GONORRHŒA.

The red cells are not affected, but in acute cases a moderate leucocytosis is present and fibrin is increased. Qualitatively, the white cells have been said by Neusser and others to show an increased percentage of eosinophiles corresponding to the large proportion of these cells in the urethral discharge. Vorbach has carefully studied twenty cases with reference to this point and finds the eosinophiles in the blood to vary from 0.5 to 11.5 per cent—averaging 4.2 per cent—within normal limits. Bettman found the eosinophiles usually increased, especially when the posterior urethra was involved. In one case with epididymitis the eosinophiles numbered 25 per cent.

## YELLOW FEVER.

Jones<sup>2</sup> found coagulation slow, the red cells *not* much diminished but showing decided degenerative changes; hæmoglobinæmia is common. He makes no observations as to the white corpuscles. Pothier of New Orleans, studying the epidemic of 1897, found the following results in 154 cases. The red cells were never considerably diminished. The leucocytes varied from 4,600 to 20,000—averaging about 9,000—hæmoglobin usually diminished at the height of the disease 50 to 75 per cent. Normoblasts were noted in a few specimens.

A case recently observed at the Massachusetts General Hospital showed two days before death 7,800 leucocytes, 92 per cent of hæmo-

<sup>&</sup>lt;sup>1</sup> Archives for Derm. and Syphil., vol. 49.

<sup>&</sup>lt;sup>2</sup> Journal of the American Medical Association, March 16th, 1895.

globin, with an absence of the typhoid serum reaction. Through the kindness of Dr. Pothier I have been able to study cover slips from twelve cases of yellow fever from the Charity Hospital of New Orleans. The differential counts of leucocytes are as follows:

	I.	II.	III.	IV.	v.	VI.	VII.	VIII.	IX.	X.	XI.	XII.
Polymorphonuclear neutro- philes Small lymphocytes Large lymphocytes Eosinophiles Myelocytes		74 22 2 2 2	93 15 2	86 11 2 .5 .5	87 8 5 	88 4 8 	97 3 	84 5 11 	86 4 10 	84 6 6 	77 4 18 1	73 20 6 1

Red cells showed nothing except in Case VIII., in which there were marked deformities and a few normoblasts. In some cases there was a marked leucocytosis, in others none. (For serum reactions, see page 458).

### TYPHUS FEVER.

Ewing' in four cases found no leucocytosis. Tumas² found no leucocytosis, as the following case shows:

	Date.		Day of disease.		Red cells.	Per cent	White cells.
Date.		disease.	A.M.	P. M.		hæmoglobin.	
January	4th	4th.		40.0			
"	5th	5th.	39.2	39.6	4,440,000	80	9,600
44	$6 ext{th}\dots$	6th.	39.0	39.5	4,220,000	77	4,800
"	7th	7th.	39.0	40.0			
46	8th	8th.	39.2	39.3	4,280,000	77	3,200
44	9th	9th.	39.0	39.5			
44	10th	10th.	38.8	39.2	4,440,000	77	3,200
44	11th	11th.	38.3	39.3			
46	12th	12th.	39.0	39.2	4,380,000	80	1,600
44	13th	13th.	38.8	39.5	4,780,000	80	3,200
46	14th	14th.	38.7	39.0			
66	15th	15th.	38.0	38.7	4,960,000	80	1,600
44	16th	16th.	38.1	38.8			
66	17th	17th.	38.7	38.6	4, 160, 000	70	4,800
66	18th	18th.	37.7	38.2			
66	19th	19th.	36.6	38.5	[3,820,000]	67	1,600
46	20th	20th.	38.1	38.3			
46	21st	21st.	37.5	38.1	[3,450,000]	62	3,280
66	22d	22d.	38.1	37.8	3,450,000	60	3,200
66	23d	23d.	37.5	38.0			
66	24th	24th.	37.4	38.0	3,130,000	50	3,200
44	25th	25th.	37.4	39.3			
66	26th	26th.	39.2				
Died or	n the 26th.						

<sup>&</sup>lt;sup>1</sup> Ewing: New York Medical Journal, December 16th, 1893.

<sup>&</sup>lt;sup>2</sup> Arch. f. klin. Med., vol. xli., p. 363.

On the other hand, Everard and Demoor, and Wilks found leucocytosis.

### MALTA FEVER.

According to the article in Allbutt's recent "Text-book of Medicine" the red cells fall gradually in the course of the fever from 5,000,000 to about 3,500,000. Bruce finds the leucocytes normal in most cases. (See also page 466.) Charles makes the amazing assertion that at the height of the fever polymorphonuclear neutrophiles are entirely absent from the blood and only lymphocytes to be found. Musser and Sailer report a prolonged case with no important changes in the blood. The serum reaction with the *Bacillus melitensis* has been obtained in cases of Malta fever by Musser, by Cox, by Curry (18 cases), and in Osler's clinic.

#### GLANDERS.

Christol and Kiener' reported leucocytosis in glanders. In a fatal case of acute glanders with autopsy which was recently studied at the Massachusetts General Hospital the following counts were recorded:

October 24th, 1897. Leucocytes, 13,600; hæmoglobin, 100 per cent.

October 31st, 1897. Leucocytes, 11,600.

November 4th, 1897. Leucocytes, 13,000.

November 9th, 1897. Leucocytes, 12,600. November 12th, 1897. Leucocytes, 12,400.

Serum reaction absent; fibrin increased; pure culture of glanders bacilli from abscesses; 86 per cent of the leucocytes were polymorphonuclear; eosinophiles absent.

The bacilli of glanders can occasionally be cultivated from the blood.

### THE BUBONIC PLAGUE.

In 1895 Aoyoma, a Japanese observer, studied the blood of this disease. He found the bacilli peculiar to the disease by cover-slip

<sup>&</sup>lt;sup>1</sup> Annales de l'Institut Pasteur, February, 1893.

 $<sup>^2</sup>$  Ref. in Sajous' Annual, 1895.

<sup>&</sup>lt;sup>3</sup> Lancet, July 30th, 1898.

<sup>&</sup>lt;sup>4</sup> Comptes Rendus de l'Acad. des Sciences, November 23d, 1868.

<sup>5 &</sup>quot;Mittheilungen aus d. Med. Fac. d. Kaiserlich Japanischen Universität," vol. iii., No. 2. Tokyo, Japan, 1895.

preparations from the blood. The red corpuscles were not altered except that their number per cubic millimetre was at times increased (e.g., 7,600,000, 8,190,000). The cause of this I do not know, but it accounts for part of the leucocytosis. The white corpuscles showed a marked increase—20,000 to 200,000 (!) per cubic millimetre. This leucocytosis was made up almost wholly of polymorphonuclear leucocytes; the eosinophiles were markedly diminished, and the blood plates were increased. The Austrian Plague Commission found only a moderate leucocytosis in most cases.

### ACTINOMYCOSIS.

Ewing (*loc. cit.*) reports leucocytosis (21,500) in a single case affecting the lungs, and Schmidt gives the following:

Date.	Red cells.	White cells.	Per cent hæmoglobin.
October 6th	3,170,000	12,000 14,500 19,700	35
" 26th	3,200,000	22,900 18,900	38 23

In two cases of actinomycosis occurring at the Massachusetts General Hospital the following counts were recorded:

Case.	Location of the disease.	Leucocytes.	Remarks.
1	Liver	31,700 28,400	June 18th, 1897. " 19th.
2	Lungs	$28,200 \\ 20,900 \\ 23,000$	" 25th. Autopsy. April, 1897. August, 1899. Autopsy.

### EPIDEMIC DROPSY.

# (Acute Anæmic Dropsy.)

MacLeod, in Vol. III. of Allbutt's "System of Medicine," describes under this title a disease not uncommon in India and other tropical countries. The blood shows a marked and constant anæmia with leucocytosis and an "increase of granular or molecular matter in the serum." Dr. Green, of the United States Marine Hospital service, recently wrote me an account of two cases strongly resem-

bling MacLeod's description of epidemic dropsy; these cases were observed by Dr. Greene at Key West, Fla. One was fatal and the other ended in recovery. The blood of both cases was notable in that the corpuscles were almost invariably oval instead of round, reminding him of the blood of amphibia. He was good enough to

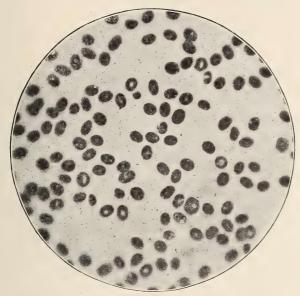


Fig. 33.—Blood in Epidemic Dropsy. Note oval shape of corpuscles. Magnified 350 diameters.

send me preparations of the blood; a microphotograph of one of them is here reproduced. Rouleaux formation was absent, another point in common with amphibian blood. There was no apparent increase of the leucocytes when I saw the blood, late in the convalescence of the second case. (On the significance of oval forms, see p. 85.)

### TETANUS.

In two (fatal) cases of tetanus treated with antitoxin, I observed the following counts:

		White cells.	Hæmoglobin.
Case I. June 2	1st, 1897	11,100	70 per cent.
June 2	3d, 1897	11,900	-
" II		19,600	

The eosinophiles do not decrease as in most fevers.

### BERI-BERI.

In a single afebrile case seen at the Massachusetts General Hospital the following is recorded: Red cells, 3,896,000; white cells, 7,800; hæmoglobin, 48 per cent.

The eosinophiles are said to be much increased in the acute stages. Spencer' states there is no leucocytosis. Ewing and Daubler, each in 3 cases, found normal leucocyte counts with moderate anæmia and no eosinophilia.

### RELAPSING FEVER.

(See page 422.)

- (a) Diagnosis. Leucocytosis is the rule. It is most marked just after the crisis. In countries where this disease is common the difficulty in diagnosing cases between attacks (when the spirochætes are absent from the blood) is frequently met with. Löwenthal has perfected a method by which in most cases the diagnosis can be made by means of the effect of the serum of suspected cases on the spirochætes of other active cases. The organism cannot be cultivated as yet, so that a diagnosis of this kind is possible only during epidemics when fresh blood containing the organism can be obtained. A drop of blood from the suspected case is mixed with a drop from a patient then undergoing a paroxysm, and the two are sealed with wax between slide and cover-glass and left in the thermostat for half an hour together with a mixture of normal blood and blood containing spirochætes as a control. At the end of that time, if the case be one of relapsing fever, the organisms in contact with the blood from that case cease their motion, while those in the control are lively. It is not a clump reaction but a direct bactericidal effect which persists in the serum nearly up to the time of the next attack. The diagnosis so made by Löwenthal in forty cases was verified in every case by the course of the disease. In this way mild or abortive cases with few organisms in the blood can also be identified.
- (b) Prognosis. If the above bactericidal power lasts as late as the seventh day from the last attack, and in sufficient intensity to immobilize the spirochætes in one hour or less, there will be no relapse. If these conditions are not fulfilled, relapse is sure to follow unless prevented by treatment. Löwenthal has verified this prognostic use of the serum in over one hundred cases.

<sup>&</sup>lt;sup>1</sup> Lancet, January 2d, 1897.

## CHAPTER V.

## DISEASES AFFECTING THE SEROUS MEMBRANES.

Tuberculous affections of serous membranes have been dealt with elsewhere (p. 280); but an exception was there made of pleurisy, for although there is reason to believe that the majority of cases of serous pleurisy are due to tuberculosis, we rarely have proof of it, and most observations upon the blood of pleurisy have not been accompanied by bacteriological examination of the effusion. Tuberculous cases have not always been distinguished from non-tuberculous. Hence the two are necessarily considered together here.

### SEROUS PLEURISY.

Von Limbeck finds in non-tuberculous cases from 13,000 to 15,000 leucocytes per cubic millimetre. The red cells and hæmoglobin are not much affected except in chronic cases.

Rieder finds in non-tuberculous cases during the stage of fever moderate leucocytosis, 13,000 in one case in which the bacteriological examination showed the presence of Fraenkel's diplococcus in the exudation. After the fever has subsided the leucocytosis falls to, or nearly to, normal, so that cases examined for the first time some weeks after onset would show no increase at all. This he thinks explains the results of Halla and others who found no leucocytosis in serous pleurisy. According to Rieder the presence or absence of leucocytosis depends not so much on whether the product is serum or pus as on whether the trouble is stationary or advancing.

In tuberculous pleurisy despite fever Rieder found but 4,600 white cells in one case, and Pick got similar results in two cases.

Hayem makes no clear distinction of tuberculous and non-tuberculous cases, and states that "acute inflammatory" pleurisy has from 7,500 to 12,000 leucocytes per cubic millimetre. The fibrin network is much less dense than in pneumonia; in most of the tuberculous cases it is not increased at all.

Morse reports 224 counts in 20 cases of serous pleurisy-9 of

them tuberculous. No relation could be established between the number of leucocytes and the presence, absence, or degree of fever, the presence of blood or microscopic pus in the fluid, the amount of fluid or the duration of the illness. Increase or decrease in the amount of fluid was not accompanied by any parallel change in the circulating leucocytes.

Only 10 of the 224 counts were over 11,000, and 9 of these 10 were in a single case which was shown at autopsy to be complicated by a secondary pneumococcus infection. Morse concludes that primary serous pleurisy does not show a leucocytosis. His figures are as follows:

From	3,000 to	4,000		 	 	. 2	cases.
46	4,000 "	5,000		 	 	. 19	66
46	5,000 "	6,000	·	 	 	. 40	×6 ,
44	6,000 "	7,000		 	 	. 31	* 46
66	7,000 "	8,000		 	 	. 50	44
46	8,000 "	9,000		 	 	. 42	44
66	9,000 "	10,000		 	 	. 27	44
66	10,000 "	11,000		 	 	. 8	46
66	11,000 "	12,000					66
66	13,000 "	14,000	,	 	 ٠.	. 1	66
	Total.			 	 	.224	cases.

The following chart (Morse) shows how "the white count dodges up and down without the slightest apparent connection with the quantity of fluid."

In 242 cases examined at the Massachusetts General Hospital the count of leucocytes was:

TABLE XXIV.—PLEURITIC EFFUSION (SEROUS).

Between	3,000 and	4,000	4 cases.
44	4,000 ".	5,000	11 "
*6	5,000 "	6,000	30 "
66	6,000 "	7,000	29 "
66	7,000 "	8,000	26 "
46	8,000 "	9,000	40 "
"	9,000 "	10,000	29 "
46	10,000 "	11,000	27 "
. "		12,000	
46	,	15,000	
Over	15,000		10 "

Total ...... 242 cases.

Average = 6,130.

Here tuberculous and non-tuberculous cases are not distinguished, and a majority of them were not seen till the trouble had been going on two or three weeks. The patients did not seek advice until the effusion was large enough to cause dyspnæa. Of the 242 cases

all but 35 had no leu-cocytosis. Most of the cases were afebrile or nearly so. Eight cases reacted to injections of tuberculin. None of these eight had leu-cocytosis.

The cases with leucocytosis were mostly those seen in the febrile stage, near the beginning of the sickness. No differential counts were made.

In chronic cases the red cells are said to be considerably diminished, but this has not been the case in our series: no count of

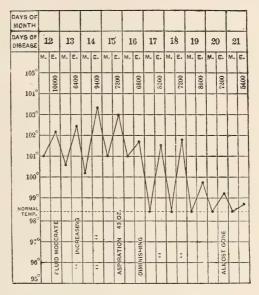


FIG. 34.

under 4,000,000 was recorded, and the coloring matter was not much diminished.

# Summary.

- 1. Red cells and hæmoglobin show no important changes.
- 2. In adults the white cells are probably never steadily increased as a result of simple uncomplicated serous pleurisy. Occasional waves of leucocytosis occur in a small percentage of cases, but even then the leucocyte count rarely reaches 14,000. Continuous leucocytosis indicates some complication.

# Diagnostic Value.

The blood count may help a good deal in doubtful cases by excluding empyema, pneumonia, and malignant disease of the lung, all of which are accompanied by high leucocyte counts. Compare the average count in serous pleurisy, 6,130, with the average in pneu-

monia, 24,000, or in empyema, 18,300. The few counts I have seen of malignant disease of the lung have been still higher.

Hayem insists, rightly it seems to me, that clinicians could get real help from blood examination in almost every case of doubtful diagnosis in which the lung and pleura are in question. In children the leucocytes are sometimes considerably increased by even a serous inflammation, their blood reacting always more strongly than that of adults to any morbid influence, and in them it may be impossible to distinguish serous from purulent pleurisy.

## PURULENT PLEURISY (EMPYEMA).

The counts in twenty-six cases observed at the Massachusetts Hospital are as follows:

TABLE XXV.—EMPYEMA.

_						
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	12			57,800 54,400		
2	2		5,440,000	55,000 49,200	51	Streptococcus.
3	1			45,500 37,700		Pneumococci in pus.
4	2		3,032,000	31,700 45,000	35	
4	~		5,052,000	34,000	99	Fifth day.
5	4			40,000 $44,000$		Eighth day. First day.
				24,400 23,000		Third day. Fifth day.
				20,000 24,000		Eighth day. Tap. Eleventh day.
				31,400 $22,000$		Fourteenth day. Seventeenth day.
0	20			41,500	60	
6	20			$41,000 \\ 29,900$		February 11th. Tap. February 15th. Tap.
7 8	21 5			$38,000 \\ 37,800$		
9	32			$35,600 \\ 35,200$		
10	4		6 000 000	34,500		
11	4		6,000,000	$32,000 \\ 30,400$		
12	47			30,000 39,000		First day. Third day.
				27,000 $26,000$		Sixth day. Eighth day. Pneumococci in pus.
13	38			30,000		The state of the s

# PURULENT PLEURISY (EMPYEMA).

TARLE XXV.—EMPYEMA (Continued).

			1			1
No.	Age.	Sex.	Red cells.	White celis.	Per cent hæmo- globin.	Remarks.
				24 000		
14	26			24,000		
				21,000	4~	
				22,800	45	T. 711
				22,800		June 5th.
				34,700		June 7th.
				29,800	• •	June 8th. Tapped turbid serum.
				17,700		June 9th.
				22,000		June 10th.
				$\begin{vmatrix} 22,100 \\ 21,800 \end{vmatrix}$		June 12th. June 14th.
				17,200	• •	June 22d.
				27,300		June 24th.
				30,100	• •	June 29th.
				25,800	• •	July 8th.
				22,600	• •	Pneumococcus.
15	6			21,600	• • •	Pneumococcus.
10		• • •		34,500		Five days later.
				20,600		January 5th.
				14,700		January 7th.
				11,400		January 23d.
				11,700		January 26th. Tapped.
				18,000		January 30th. Re-accumulation.
				26,000		February 3d. Operated; pneu-
				,		mococci and streptococci.
16	2			19,600		and the procession
17	45			18,700		Friedländer's bacillus.
18	6			16,900		Tap, pus.
19	24		4,152,000	15,000	45	Operated.
20	27			14,200		
21	39			13,300		Gangrene of lung also.
				14,900		Fifth day.
	0.0			22,800		Fifteenth day.
22	30			13,000		O
23	8			13,000		Sterile.
24	22			12,700	1:	Tuberculous.
			4,192,000	10,800	48	December 20th.
				18,500		December 22d. Broke into lung;
				14 500		cultures sterile.
				14,500		January 2d.
				18,300	• •	January 4th.
				$10,000 \\ 16,200$	50	January 9th. Pneumococcus.
				15,500	00	I neumococcus,
				15,300		
			4,500,000	14,000		
			4,850,000	12,650	85	
			2,000,000	12,450	60	
			4,000,000	12,000	- 00	
			_, 000,000	11,700	44	Cultures sterile.
				10,900		3200 00022201
25	71			8,400		Three quarts sterile pus.
				7,600		Operated; several pints of pus;
26	45			6,500		streptococci.
_						

This is in marked contrast with serous pleurisy as above noted. Von Limbeck noticed the same thing.

(Ewing:) "In a case of empyema, in which tubercle bacilli were extremely numerous, the writer found moderate intermittent leucocytosis (maximum 18,000)."

#### PERITONITIS.

A patient with serous pleurisy (non-tuberculous) is hardly ever in danger, while if the general peritoneal cavity is the seat of a like inflammation, recovery is almost out of the question.

This clinical difference is parallel to the difference in the blood condition. Any inflammation of the peritoneum (non-tuberculous), whether serous or purulent, calls very large numbers of leucocytes into the peripheral blood. The only exceptions to this rule are those cases in which the organism is so overwhelmed by the disease that it offers no resistance. We have seen that this same effect is produced in the severest cases of pneumonia and diphtheria, and presumably it is true of many other infectious diseases in which the blood has been less carefully studied.

Almost all cases of general septic peritonitis show very marked leucocytosis, and the spreading of a localized process is always indicated by an increasing leucocytosis. But here and there it happens that the patient cannot react against the disease at all, and then the leucocytes are normal or diminished. This never occurs in empyema, because the system is never so overwhelmed by a septic process in the pleura. The fibrin network is increased in almost all cases. The following counts, all in fatal cases, illustrate these points:

TABLE XXVI.—GENERAL PERITONITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1 2	34	F.	4,860,000	54,000		Abscess of spleen (?).
2	Adult.	F.	7,000,000	32,000		Purulent: from appendix-myelocytes,
3	15			28,000		2 per cent. General septic.
4	27			23,000 27,800	68	Next day.
4	21			23,000		December 6th. Epigastric.
.			4,004,000	34,200	53	December 17th.
5	28			24,100 17,800		Pelvic, after abortion. Seventh.
6	27	M.	5,317,000	24,000	75	Dysentery, with perforation.
67	22			23,200		Gastric ulcer; perforation; operation.  Death.

TABLE XXVI.—GENERAL PERITONITIS (Continued).

No.	Age.	Sex.	Red cells.	White Cells.	Per cent hæmo- globin.	Remarks.
8 9 10	Adult. 31 Adult.	F. M. M.	4,000,000	22,000 19,000 16,000		Chronic, purulent. Ruptured bladder. Moribund.
11	29			13,000 25,800		First day. Rupture of gall bladder. Second day. Died.
12	21	М.		12,200 9,000		June 30th. July 2d. Autopsy.
13	32			11,000 8,300		October 27th. Circumscribed. November 2d.
14	26			7,400 9,700		July 19th. July 28th.
15 16	60 Adult.	m.	6,000,000	6,000 6,000		Purulent; operation. Death.
17	52	F.		5,328		Obstruction; died in three days; autopsy.
18 19	Adult.	M. F.	5,760,000 6,840,000	5,300 4,600	95	Purulent. Death within 24 hours.
20	••••			Marked increase.	*****	After appendix operation. Diff. 1,000 cells: Polymorphonuclear cells, 90.5 per cent; lymphocytes, 9.5; eosinophiles, 0; myelocytes, 1.
21	38	F.		1,700! 2,100!		August 2d. Autopsy. August 3d.
22	27	•••		1,600		General. Gastric ulcer.

## Diagnostic Value.

1. When a diagnosis rests between peritonitis and (a) obstruction (non-malignant); (b) malignant disease; (c) hysteria, phantom tumors or malingering, the presence of marked leucocytosis with increase of the fibrin network speaks strongly in favor of peritonitis.

Obstruction or malignant disease may increase the number of leucocytes, but rarely increases the amount of fibrin.

Hysterical or malingering patients have normal blood.

- 2. We cannot distinguish serous from purulent peritonitis in septic cases, but *tuberculous peritonitis* can always be excluded if leucocytosis is present.
- 3. As to the "chronic granular peritonitis," non-tuberculous and non-septic, I have seen no reference in hæmatological literature and have no first-hand knowledge.
- 4. In the *worst* cases leucocytosis may be absent, as in the most virulent type of pneumonia.

# PERICARDITIS (WITH EFFUSION).

As in most other inflammations of serous membranes we can distinguish the tuberculous cases which have no leucocytosis from the rheumatic or septic cases which always increase the white cells.

The tuberculous cases are discussed under tuberculosis (see p. 285). The following counts illustrate the rheumatic form of the disease:

TABLE XXVII.

Case.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1		42,400		November 3d, 1895.
		32,600		November 7th, 1895.
		19,200		November 11th, 1895.
		17,500		December 8th, effusion nearly gone.
2	2,632,000	21,600	45	December 24th, endo pericarditis,
	,,	,		chronic nephritis.
		27,100		December 26th.
		36,600		December 29th, no fever.
		26,700		May 1st.
	1	19,200		May 3d.
		24,800		May 4th.
		28,600		May 7th.
		20, 100		May 8th.
3	4,568,000	26,000	67	December 14th,
	_,,	19,400		December 20th, effusion subsiding.
4		24,000		200022001 100121, 0240202 1440202
$\frac{4}{5}$	4, 168, 000	19,447	67	
$\ddot{6}$	2,200,000	15,400		
7		14,600	65	Autopsy.
8		12,000	63	Tapped.
		,,,,,,		

Hayem has noted that pericarditis is far more apt to produce leucocytosis than is endocarditis.

# Diagnostic Value.

In excluding cardiac hypertrophy or simple dilatation with ruptured compensation, both of which may occasionally simulate a pericardial effusion, the presence of marked leucocytosis is absolutely decisive. When we are sure that effusion exists, the absence of leucocytosis points strongly to a tuberculous process as its cause.

### MENINGITIS.

Leucocytosis is usually well marked. Von Limbeck considers that tuberculous meningitis can be distinguished from purulent by the absence of leucocytosis in tuberculous cases, but Osler' states that many cases of tuberculous meningitis do have leucocytosis throughout their course, and my own observations (see Table XXVIII.) tend to confirm this. Of Rieder's cases, one had leucocytosis and one did not. Zappert's case had 11,130 white cells, and Ziemke one with 17,500. It seems, therefore, that we sometimes have here an ex-

<sup>&</sup>lt;sup>1</sup> "Practice of Medicine." 2d edition.

ception to the rule that tuberculous processes do not produce leucocytosis. Certainly some cases do follow this rule. But however this may be, it is certain that purulent meningitis, whether secondary or of unknown origin, is characterized by high leucocyte counts, and if in a case evidently of meningitis of some kind leucocytosis is absent, the case is probably tuberculous in origin.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1 2	19 Adult.	й.	5,900,000	62,000 40,000		Autopsy; pneumococcus. Diff. 1,000 cells: Adult cells, 93 per cent.; young cells, 7; eosin-
3 4	23	M. M.	6,400,000 6,000,000	33,000 $27,500$ $16,500$	95	ophiles, 0. (Otitis?) question of typhoid. March 16th; cerebro-spinal.  "18th.
5 6 7	15 "	F. M.	5,020,000	27,000 19,500 16,000	73	Tuberculous; no autopsy.
8 9 10	26 20 2	M. F. M.		16,000 15,784 14,200		Autopsy; cerebro-spinal. Basilar; no tuberculosis in family;
11 12	22 35	M. M.	4,356,000	14,000 11,700	72	had pneumonia.
13	26	M.	5,040,000	11,200		Specific.

TABLE XXVIII.—MENINGITIS.

Cerebro-spinal meningitis (see Cases 4 and 9, Table XXVIII.) shows the same characteristics in the blood as do cases limited to the cerebral meninges. A case reported by v. Jaksch had 4,800,000 red and 24,000 white cells.

#### EPIDEMIC CEREBRO-SPINAL MENINGITIS.

Williams finds leucocytosis in about two-thirds of his cases.

The following counts were made during the epidemic of 1897. The red cells are not markedly affected. Vasomotor polycythæmia may occur. Leucocytosis is the rule, but is not invariable. In a general way the higher the count the severer the case, and the count usually rises as the case gets worse and falls with improvement, though often very slowly. In the febrile recrudescences so common in chronic cases, the leucocytes usually rise again, though the eosinophiles may not disappear as they ordinarily do in the ear-

<sup>&</sup>lt;sup>1</sup> Zeit. f. klin. Med., 1893, p. 187.

liest days of the illness. No prognostic inferences can be drawn from the behavior of the eosinophiles in meningitis.

TABLE XXIX.—EPIDEMIC CEREBRO-SPINAL MENINGITIS. White cells. Between 5,000 and 10,000 ..... 10,000 " 15.000 20,000 25.000 " 30,000 " 35,000 40.000 " 45.000 " 50.000 " 

Flexner and Barker, investigating a large epidemic at Lonaconing, Md., found leucocytosis in every case (12,000–32,000 per cubic millimetre). The epidemic studied by Williams and myself was apparently due to the diplococcus intracellularis of Weichselbaum. Secondary meningitis (otitis media, etc.) seems to have similar effects on the blood.

# Diagnostic Value.

Meningitis is the only intracranial disease (except abscess and apoplexy) which shows leucocytosis, and this fact may be of great help in excluding other causes of coma.

- 1. Brain tumor, hysteria, lead encephalopathy, and most cases of narcotic or alcoholic intoxication do not cause leucocytosis and hence can be excluded by its presence.
- 2. Uræmia, apoplexy, sun-stroke,¹ diabetic coma, and post-epileptic coma may have leucocytosis and cannot be distinguished from meningitis when leucocytosis is present; but the absence of leucocytosis excludes meningitis.
- 3. Some cases of typhoid, when seen for the first time and without a history of the previous illness, may be difficult to distinguish from meningitis, but typhoid never has leucocytosis if uncomplicated and meningitis always has.
- 4. From pneumonia we cannot distinguish meningitis by the blood count.

<sup>1</sup> In a case of heat exhaustion (temperature 104°) without coma, a leucocyte count of 27,200 is recorded at the Massachusetts General Hospital.

# PART III.

## CHRONIC INFECTIOUS DISEASES.

## CHAPTER VI.

## TUBERCULOSIS.

RED CORPUSCLES AND HÆMOGLOBIN.

(a) Quantitative Changes.

I. The striking fact is the absence of such anæmia as we should expect, judging from the pallor of the patients and the nature of the disease. It is common to find a normal or even increased number of red cells in pale cachectic-looking consumptives. We cannot help wondering whether our methods of examination are at fault, that is, whether the drop we examine is typical. (For discussion of the subject see p. 72.) However this may be, it is undoubtedly the fact that in most cases of tuberculosis, even in advanced stages, the count of red cells is approximately normal. Often the hæmoglobin is also high.

II. In a smaller number of cases the hæmoglobin is much diminished, although the count of red cells is normal—in other words, we find the blood characteristic of a moderately severe secondary anæmia. The red cells are numerous enough, but only because their numbers have been recruited by the influx of "half-baked" or decrepit corpuscles, small-sized and pale, poor in albumin and hæmoglobin.

The condition differs from that of chlorosis mainly in that some of the red cells are normally developed and nourished, while in chlorosis all, or nearly all, are feeble. Such blood occurs in the severer and more cachectic sufferers from tuberculosis, just often enough to make us wonder that it is not always to be found.

III. In a small percentage of cases both red cells and hæmo-

globin are considerably diminished, the latter usually suffering more than do the actual number of cells, that is, the color index is usually below 1.

Von Limbeck has recorded a case in which in the course of a tuberculous process (acute miliary) the red cells fell as low as 730,000 (white cells, 4,300; hæmoglobin, twenty-five per cent). But the account of the blood is not sufficiently explicit in this case to enable us to exclude a true pernicious anæmia in the course of which the tuberculosis may have been only the last incident. No other such case is on record, so far as I am aware.

(Ewing:) "In phthisis as well as in other tuberculous processes, great caution must be used in judging of the patient's improvement from an increase in red cells or hæmoglobin. The writer has seen the hæmoglobin and red cells increase while the patient was rapidly losing flesh, the lesions advancing, and the total quantity of blood doubtless falling. In several of Bierfreund's cases the hæmoglobin steadily increased while the patient was developing general tuberculosis."

IV. Fibrin is not increased unless extensive secondary infection is present.

# (b) Qualitative Changes.

- I. There may be none whatever.
- II. There may be only a pallor of some of the individual corpuscles with slight changes in size and shape.
- III. In very severe cases the poikilocytosis may be extreme, but this is much rarer than in many other cachexias of the same severity (e. g., malignant disease).
- IV. An important point is the usual absence of nucleated red cells. Even after hemorrhages it is rare to find any nucleated red cells, and this is in marked contrast with cancer cases, in which nucleated red cells are the rule.
- V. The degenerative changes described by Maragliano are sometimes found in severe cases with mixed infection (vide infra).

As regards the influence of the different seats of tuberculous disease (meningeal, pulmonary, genito-urinary, acute miliary, etc.) upon the red corpuscles and hæmoglobin the following are the probabilities.

Pure tuberculous disease itself, whatever its seat, has little or no effect upon the blood. The widely different conditions of the blood

found in different cases depend probably on the presence or absence of various other organisms (diplococcus lanceolatus, pyogenic cocci) associated with the tubercle bacillus, and on whether there is some drain on the body albuminoids (diarrhea, peritoneal effusion, starvation, prolonged suppuration). When the infection is a mixed one, the blood shows the ordinary effects of septicæmia (for then the case is practically one of septicæmia) in lessening the number and quality of the red cells. When there is drain on the fluids and proteid constituents of the body, the red cells may not seem to be diminished, owing to the concentration of the blood from loss of fluid. Under such circumstances they may even seem increased, but the individual corpuscles are sure to be lacking in hæmoglobin and the other nitrogenous bodies of which they largely consist.

Fever may be present without there being any changes in the red cells that we can detect. It is only septic fever, and not the fever of pure tuberculosis, that drains the corpuscles of their vitality and lowers their numbers.

### LEUCOCYTES.

## (a) Quantitative Changes.

Here, as with the red cells, the striking fact is the absence of changes in pure tuberculosis. It makes no difference whether we are dealing with tuberculosis of the bones, serous membranes, or internal organs. So long as the infection remains unmixed the white cells are not increased. In certain localities (lungs, kidneys) the opportunities for a secondary infection and septicæmia are so great that we frequently find evidence of it in the blood. On the other hand, psoas abscesses before they are opened often contain only tubercle bacilli, and the blood of such cases shows no considerable changes.

So much more is known of the numerical variations of the leucocytes in tuberculosis than of the other blood constituents, that I shall give a separate account of them in phthisis, in tuberculous bone disease, in tuberculous meningitis, acute miliary tuberculosis, genitourinary tuberculosis, and tuberculous peritonitis.

## I. PHTHISIS.

- I. In *incipient phthisis* the leucocytes are normal except after hæmoptysis.
  - II. After attacks of hæmoptysis, there is usually leucocytosis,

subject to wide variations according to the amount of the hemorrhage and the resisting power of the patient.

This follows the laws of ordinary post-hemorrhagic leucocytosis (*ride supra*) and disappears quickly when the hemorrhage ceases.

III. Cavities.—Very constantly accompanied by leucocytosis. Indeed the absence of leucocytosis in any case proves the absence of any cavity of considerable size.

(Ewing:) "The writer has seen both lungs consolidated and riddled with small cavities in a case lasting five weeks, yet the leucocytes were never found above 12,000. The absence of leucocytosis in these cases of acute phthisis, which resemble pneumonia, may often be of value in diagnosis. Similarly in a case of subacute empyema in which the tubercle bacillus was largely concerned, the leucocytes were found not to exceed 14,000 during an acute febrile period."

- IV. Extensive infiltration ("tuberculous pneumonia") may cause marked increase of white cells, sometimes as great as in croupous pneumonia, but this is not invariable.
- V. Fibroid Phthisis (chronic interstitial pneumonia).—As a rule the leucocytes show no increase, but if, as sometimes occurs, we have the combination of this condition with cavity formation, the latter may increase the count of white cells.
- VI. Ferer. —When the temperature is normal, the leucocytes are normal, but a febrile state may or may not be accompanied by leucocytosis (according, presumably, as the fever is or is not due to pyogenic organisms).
- VII. Tuberculin Injections.—At the height of the reaction fever the leucocytes almost always rise, the lymphocytes and eosinophiles being relatively increased.

In a general way, the worse the case the higher the leucocyte count, yet the signs may be advanced without causing any leucocytosis if cavities are absent.

The following tables give some idea of the range of the counts in average hospital cases of phthisis:

### PHTHISIS—RED CELLS.

Between 2,000,000 and 3,000,000 = 1 case.

- " 3,000,000 " 4,000,000 = 18 cases.
- " 4,000,000 " 5,000,000 = 25 "
- 6,000,000 " 6,000,000 = 16

Total . . . . . . . . . . 60 cases.

### Phthisis—Hæmoglobin.

```
From 10 to 20 \text{ per cent} = 1 \text{ case}.
     20 4
           30
                     = 0 "
  66
     30 "
           40
                      = 4 cases.
                      = 6 "
     40 "
           50
     50 "
          60
                      = 19
     60 "
          70
                      = 23
     70 "
          80 "
                      = 16
  66
     80 " 90 "
                      = 6
    90 " 100
                      = 5
```

Total ......80 cases.

## PHTHISIS—WHITE CELLS.

Between	3,000	and	4,000 =	5	cases
44	4,000	66	5,000 =	4	46
66	5,000	44	6,000 =	9	+6
"	6,000	44	7,000 =	9	**
44	7,000	**	8,000 = 3	10	46
66	8,000	44	9,000 =	9	*6
"	9,000	44	10,000 = 1	14	+6
46	10,000	44	11,000 =	5	46
64	11,000	66	12,000 =	7	+6
46	12,000	44	15,000 = 9	25	44
44	15,000	44	20,000 = 1	16	44
46	20,000	66	30,000 =	8	44
46	30,000	66	40,000 =	3	66
	,				

Total . . . . . . . . . 124 cases.

The number of those showing leucocytosis is slightly greater than those without it, probably because incipient cases rarely think themselves sick enough to come to a hospital. On the other hand, some of the cases which appear to have been going on for months have normal leucocyte counts. The duration is less important than the nature and severity of the process. It is rare to see extensive signs in the lungs without leucocytosis—fibroid phthisis excepted.

# Qualitative Changes in the White Cells.

- 1. Many cases show none at all.
- 2. When the leucocyte count is normal we may find an increased percentage of large and small lymphocytes, such as is commonly found in any blood poor in nutritive qualities (see p. 96).
  - 3. When leucocytosis is present, we usually find the ordinary 18

marked increase in the percentage of polymorphonuclear cells at the expense of the lymphocytes.

For example: C. D--, male, thirty-two years old. Tuberculosis of lungs, with cavities; leucocytes, 17,580. Differential count of 1,000 cells shows:

	Per cent.
Polymorphonuclear	. 83.4
Lymphocytes (small)	. 8.2
Large lymphocytes (large and transitional)	. 8.4
Eosinophiles	. 0.

4. Eosinophiles are increased during the reaction from an injection of tuberculin, and also in some cases with cavities in which possibly the individual inoculates himself with tuberculin manufactured in the cavities of his own lungs.

Otherwise the eosinophiles are increased only at certain physiological seasons—menses and coitus. In most cases associated with leucocytosis they are absent.

5. Myelocytes were found by Holmes, W. R. May, and myself in many cases of advanced phthisis. They averaged .3 per cent.

# Perinuclear Basophilia.

Neusser and his followers have advanced a theory that the occurrence of perinuclear basophilia during tuberculosis is a favorable sign and marks a system capable of resisting the tuberculous infection. The researches of Futcher and my own attempts to verify Neusser's theory have not confirmed his findings.

Holmes, of Denver, has studied the leucocytes in phthisis with great care and considers that he finds therein means not only of diagnosing tuberculosis by the blood alone, but of measuring the degree of advancement of the process, and the amount of resisting power in the patient.

I have carefully followed out Holmes' procedures with stains seen and approved by him. I can verify most of his statements of fact, but some of the inferences which he draws therefrom are, I think, wholly unwarranted. The blood changes in pulmonary tuberculosis are mainly such as he describes, but they have no diagnostic value, as similar changes are found in a great variety of other diseased conditions. The increase of polymorphonuclear forms in advanced cases, the increased amount of "débris," the degenerating

forms, etc., are all characteristic not of tuberculosis alone, but of any severe suppurative process. The increase of "débris" is probably the same datum which Watkins interpreted as an increase in blood plates and Goldberger and Weiss as "extracellular glycogen." (With Holmes' "undeveloped nuclei" in the leucocytes, compare p. 110.)

### II. BONE TUBERCULOSIS.

Brown' has studied seventy-two cases, Dane' forty-one. Dane's study of the blood in forty-one cases of hip disease and Pott's disease is a very careful one. Whenever abscesses appeared in connection with the disease, cultures were taken when the abscess was first opened and again later on, and the coincidence of low counts with absence of pyogenic cocci and with high counts of secondary pyogenic infection is very notable. Dane's conclusions are as follows.

- 1. "High leucocyte counts, especially in hip disease, point to the probability that there is, or soon will be, abscess formation; but low counts do not preclude the presence of abscess, especially in long-standing cases.
- 2. "If abscess is present, a low count of white cells indicates the absence of secondary pyogenic infection (proved by cultures).
- 3. "Cases of traumatic origin are generally accompanied by a high leucocyte count.
- 4. "The leucocyte count bears no direct relation to the temperature; one case with 30,980 leucocytes (five-year-old girl) showed a temperature of only 99.4° at the time of the count. In another girl of three years whose temperature ranged between 101° and 104°, the leucocytes were only 7,224, or subnormal for that age (vide infra, p. 445).
- 5. "Cases where at the primary operation the pus proved sterile show an increase in the leucocyte count when the wound becomes infected with pyogenic organisms" (as it always does).
- 6. "The red cells are rarely diminished, but the hæmoglobin is usually relatively low (mild secondary anæmia in these cases). This absence of a diminution in the red cells in these cases is the more remarkable because they were almost all in young children whose blood is much more sensitive to any deleterious influence than that of adults."

<sup>&</sup>lt;sup>1</sup> Transactions of California Medical Society, 1897.

<sup>&</sup>lt;sup>2</sup> Boston Medical and Surgical Journal, May 28th, 1896.

Brown dissents from several of Dane's conclusions. He thinks that a case may go on to abscess formation without any increase in the leucocyte count. When an increase does take place, he thinks it due either to a secondary infection or to an increased activity of the tuberculous process itself without any secondary infection. The latter process, however, in Brown's experience causes only a moderate increase (2,000-3,000), while if a marked increase suddenly or gradually occurs he thinks it "most significant of secondary infection." With Dane's fifth conclusion he wholly agrees and adds: "After the infection (produced by the operation) the leucocytosis is very high for a time, and if the sepsis is acute and threatens life, it remains high until the crisis is passed." Otherwise it gradually falls after the first few days, and if the patient progresses well, it disappears. If the pyogenic matter overcomes the recuperative power, the leucocytes fall as in peracute pneumonia or peritonitis. In such cases the anæmia increases as well.

## Qualitative Changes.

(a) As in other forms of tuberculosis there may be none at all.
(b) The cell changes in purely tuberculous cases is illustrated well by Case 17 of Dane's series, a boy of seven whose blood on the day of operation for hip disease with large abscess showed 8,932 leucocytes. The differential count was as follows:

	Per	cent.
Polymorphonuclear neutrophiles		40
Small lymphocytes		49
Large lymphocytes and transitional forms		8
Eosinophiles		3

Eight ounces of pus were evacuated, in which cultures showed the absence of pyogenic organisms.

This case demonstrates that some cases of tuberculous suppuration have no tendency to produce leucocytosis or to increase in the neutrophiles, but influence the blood only by producing what might be termed a functional debility of the blood through lack of nutritive substances in the plasma. This condition is by no means peculiar to tuberculosis, but occurs in a great variety of debilitated or cachectic conditions, as already stated.

(e) But when a septicæmia complicates the tuberculosis, cell metamorphosis appears to be accelerated, and we get with the quan-

titative increase of leucocytes such qualitative changes as the following:

			P	er cent.
Polymorphonuclear neutrophiles	٠.		 	84
Lymphocytes (small)			 	9
Lymphocytes (large and transitional)		a- e-	 	6
Eosinophiles			 	1

This was a case (No. 33 of Dane's series) in which the abscess, sterile when first opened, had become inoculated with the staphylococcus aureus.

(d) Not every case with leucocytosis shows qualitative changes as the above. One of Dane's cases (No. 22, a boy of seven) showed a leucocytosis of 23,387, but only sixty per cent of these were polymorphonuclear, and two per cent eosinophiles.

In a case recorded by Dane (No. 32), tuberculous osteomyelitis showed 6,083 white cells (subnormal, as the child was only two years old) with sixty-four per cent of polymorphonuclear cells. The pus from the bone cavity showed no pyogenic organisms on culture. Ordinary septic osteomyelitis gives very different results (see p. 251). Dane's cases were almost exclusively hip and spinal affections.

The following cases from the Massachusetts General Hospital records illustrate tuberculosis of other bones:

Case.	Diagnosis.	Red cells.	White cells.	Per cent hæmo- globin.
1	Tuberculosis of the knee joint  Metatarsal tuberculosis  Tubercular rib	6,472,000	9,400	63
2		2,704,000	8,000	?
3		4,650,000	6,500	61
4		5,016,000	5,800	73

TABLE XXX.

## III. ACUTE MILIARY TUBERCULOSIS.

Probably there are no important changes in the red cells or hæmoglobin. The number of cases on record is too small to enable me to speak positively on this point, but the acuteness of the disease would lead us to expect the normal or approximately normal conditions recorded in the few published cases.

About the leucocytes we know more.

# Quantitative Changes.

Normal or subnormal counts are the rule. When occasionally there occurs a leucocytosis it may be inferred that the miliary process accompanies a suppurative one, and that the latter and not the former is responsible for the increased number.

Warthin' reports a case with autopsy in which he made over thirty counts of the white corpuscles, verifying the more remarkable results by repetition. Autopsy showed, besides miliary tuberculosis, a cavity in the lower lobe of the right lung and a suppurating focus about the seminal vesicles containing four ounces of pus rich in tubercle bacilli. Whether pyogenic organisms were also present is not stated. The leucocyte counts were as follows:

TABLE XXXI.

Day.		Hour.	Leuco- cytes.	Remarks.
Decembe	r 6th	10 A.M.	3,500	
66	12th	8 A.M.	5,000	
66	18th	5 P.M.	3,500	
46	22d	10 A.M.	5,625	
44	22d	11:30 а.м.	4,725	
46	22d	3 P.M.	5,000	
66	22d	5 P.M.	3,125	
44	24th	8:30 а.м.	3,750	
44	$24 \mathrm{th}$	11:30 A.M.	3,750	
44	24th	2 P.M.	2,500	
166	24th	4:30 P.M.	2,500	
44	25th	8 A.M.	1,875	[80 per cent.
44	28th	5:30 р.м.	3,750	Red cells, 4,125,000; hæmoglobin,
46	29th	10 A.M.	1,250	
66	29th	2 P.M.	1,250	
44	29th	5:30 P.M.	3,750	
46	31st	12 м.	1,250	
66	31st	6 P.M.	2,500	
January	2d	11 A.M.	1,250	
"	$^{2d}$	5 P.M.	2,500	
46	3d	2:30 р.м.	600	Severe chill. Count repeated several
				times.
66	5th	8:30 A.M.	3,750	
66	5th	11 A.M.	3,137	
66	5th	4 P.M.	8,125	Moribund.
44	6th	9 а.м.	10,000	
66	6th	10 A.M.	5,625	
46	6th	11 A.M.	2,500	
46	6th	12 м.	5,625	
66	6th	12:50 P.M.	Death.	
			!	

In another case he found also a subnormal count. Rieder found normal counts in two cases. Von Limbeck states that the leucocytes are normal, but gives no counts.

<sup>&</sup>lt;sup>1</sup> Medical News, 1895.

The following cases from the Massachusetts General Hospital records illustrate these points:

TABLE XXXII.—ACUTE MILIARY TUBERCULOSIS.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
28	М.	2,448,000	550	35	March 8th.
			1,200		March 11th.
			1,100		March 11th, gave protonuclein gr. xv.
					t.i.d.
			1,300		March 13th, differential count: Polymorphonuclear, 78 per cent. Lymphocytes (small), 12 Lymphocytes (large), 9 Eosinophiles, 1 March 14th, glands rapidly diminish-
			1,500	• •	ing. March 18th, died. Autopsy.
Ì		3,296,000	3,000	43	march forn, died. Autopsy.
24		5,200,000	3,300	40	First day.
~=			8,000		Third day.
			4,400		Ninth day.
			9.100		Twelfth day.
52	F.		3,500	90	
18	M.		3,600		Autopsy.
40	M.		3,750		Autopsy.
40			4,000		
14	F.	[3,720,000]	4,400	45	Autopsy.
26			4,600		First week.
	3.5	4 004 000	3,400		Sixth week.
51	M.	4,664,000	4,800	• •	Autopsy. Chronic phthisis also.
23	М.		4,900	65	Autopsy. Differential count normal.
18	F.		$\begin{bmatrix} 5,400 \\ 5,400 \end{bmatrix}$	80	September 21st.
10	Τ.		7,400		September 24th. No serum reaction.
29	M.		5,600	64	Autopsy. No serum reaction.
12	F.		6,100	• •	Autopsy.
19	F.		6,600		Autopsy.
56			6,800		First day.
			8,200		Ninth day.
			21,000		Day of death.
37	F.		7,500	71	Autopsy.
18			7,600		First day.
00	3.5		8,600		Fourth day. Ninth, death.
36	M.		7,600		Healed phthisis also. Autopsy.
20	F.		$7,800 \\ 7,200$		May 14th.
35		3,920,000	8,000	45	May 22d, death. Autopsy.
30		4,500,000	8,800	52	
30	M.	4,000,000	9,250		April 18th.
	1.1.		9,450		April 20th. Autopsy.
45	M.	5,237,000	10,000		Autopsy.
38			12,200		Autopsy.
22	M.		12,700		Phthisis also. Autopsy.
					* *

TABLE	XXXII.—ACUTE	MILIARY	Tuberculosis (	(Continued).
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Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
78		2,416,000	32,000	29	Diff. count 1,000 cells: Polynuclear, 87 per cent. Lymphocytes, 11 " Eosinophiles, 0 " Myelocytes, 2 " Normoblasts = 5. Megaloblasts = 2. Complicated with diphtheria.

Case I. of the above table is a striking example of the remarkably low leucocyte count sometimes seen in this disease. The counts were carefully verified by several competent observers.

## Qualitative Changes.

In Warthin's case above quoted, he repeatedly made differential counts of the leucocytes by Ehrlich's methods, with this average result:

Polymorphonuclear neutrophiles	91.49	per cent.
Lymphocytes (small)	5.52	66
Lymphocytes (large and transitional)	3.09	44
Eosinophiles	0.	44
Myelocytes	2.	

## IV. TUBERCULOSIS OF SEROUS MEMBRANES.

#### 1. Tuberculous Peritonitis.

The blood condition is exactly as in other forms of tuberculosis, except in so far as it is modified by the drain exerted on the blood by diarrhea or by transudation or exudation into the peritoneal cavity. Such events concentrate the blood by withdrawing water and albumin from it and may give us a normal number of red cells per cubic millimetre, when in reality a considerable anæmia is present. As a rule, the blood shows a mild secondary anæmia without leucocytosis or with leucopenia. This is exemplified in the following table from the Massachusetts General Hospital records:

TABLE XXXIII.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
26	F.	3,120,000	2,240	58	
28 33	F.	2,900,000	$\frac{2,600}{3,800}$	48	
24	M.	5,360,000	3,800	10	January 6th, 1896.
~ 1	2,2,	5,760,000	5,600	85	April 13th, 1896.
25	F.		3,900		Tuberculous tube.
21	М.		4,400		
25			4,700	52	
27	М.		4,900	64	March 1st.
49	Nr.		5,500		March 9th.
43	М.	4,560,000	$5,000 \\ 3,250$	76	December 18th, 1895.
30	F.	4,500,000	5,280 $5,180$		January 10th, 1895. Tuberculous tube.
20	F.	5,936,000	5,400		Tuberculous tube.
28			5,400		
44	M.	2,974,000	5,530		Pleuritic effusion also.
24			5,600		
34			5,600		
16	F.	3,840,000	6,000		
33 37	F.	4,000,000	$6,000 \\ 6,200$		
51			5,400		
50	F.	5,240,000	6,400		
13		0,010,000	6,400	55	
37	М.		6,700		May 22d, 1896.
22		3,552,000	6,800	45	
15		5,112,000	6,900	70	Polynuclear, 44 per cent; lympho-
19			7,200		cytes, 49 per cent; eosinophiles,
16			7 400	70	7 per cent.
15			$7,400 \\ 7,400$	10	
23			6,800		
33	i.		7,900		
31			8,000		
16			8,700		First day.
			7,600		Thirtieth day.
15			9,800		
19 20			9,800 $10,800$		
47			11,300		
19			11,600	65	
37			12,400		
19			14,500		
	!		11,600		
15	• •		14,600		First day
16			16,100		First day.
			14,200 11,000	• •	Sixth day. Eighth day.
6		4,576,000		52	Intestines perforated.
,		2,010,000	31,900	0.0	Ninth day, after two dry taps.
			18,500		Thirteenth day, pus and fæces coming
				45	through tap holes.
			22,900		Seventy-eighth day. Autopsy.
	t	1		i	

Table XXXIII. (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
			7,000		May 30th, 1896.
30	M.	5,560,000	6,800		
44	F.		7,000	73	
26	M.	4, 368, 000	7,400	45	
17	M.	4,904,000	8,000	75	
32	F.		8,200		
20	F.	4,200,000	8,500	58	Tuberculous tube.
$\tilde{29}$	F.	3,400,000	8,600	30	Tuberculous tube.
50	F.				
		4,600,000	10,000	50	
41	M.	5,200,000	10,000		
38	F.	4,816,000	11,200		
21	F.	3,555,000	11,500	65	
27	F.		16,900	76	Pelvic abscess also.
			18,300	. 0	CITIO HOBOURG AISO.

I know of no differential counts of leucocytes in tuberculous peritonitis. Presumably the sluggish metabolism of the cells found in other forms of pure tuberculosis exists here and causes an excess of the mononuclear elements.

#### 2. Tuberculous Meningitis.

Remarkably few counts are on record so far as I can ascertain. Von Limbeck gives but a single case (with autopsy). Four counts, the last on the day of death, showed the following:

May	22d,	1889:	Leucocytes		 	٠, ٠							8,000
46	23d,	1889:			 								8,000
66	24th,	1889:	66		 								6,000
44	26th,	1889:	44		 								7,500

Rieder records two cases, in one of which the leucocytes were "normal or subnormal, in the other increased." In both diagnosis was confirmed by autopsy. The counts in these cases were as follows:

Case I.—February 26th, 1891: Leucocytes	7,800
March 2d, 1891: Leucocytes	5,900
Case II.—May 30th, 1891: Leucocytes	14,400

Türck studied three cases, all showing more or less leucocytosis (9,600 with 90 per cent polynuclears and no eosinophiles, 17,100 and 18,100 with 83 per cent polynuclears and no eosinophiles, 20,800 with 86 per cent polynuclears and no eosinophiles). Blood plates and fibrin were not increased.

## Pick ' saw two cases:

Case I.—February 28th, 1890: Leucocytes	6,500
March 5th, 1890: Leucocytes	8,000

In the second case there was also no leucocytosis. Autopsy in both. Sorensen's two cases showed respectively 8,300 and 9,400 leucocytes. My own results in twenty-seven cases are as follows:

TABLE XXXIV.—TUBERCULOUS MENINGITIS.

Age.	sex.	Red Cells.	White cells.	Per cent hæmo- globin.	Remarks.
2			29,900		,
$\frac{2\frac{1}{2}}{2}$	М.		28,000 34,300	63	July 8th. July 9th. Autopsy.
2	F.		25,900 23,800		May 30th. June 4th. Tuberculous peritonitis
			32,800 27,800 23,600 16,500 21,000 19,800		June 8th. June 10th. June 12th. June 14th. June 16th. June 18th.
11			24,800 32,700 32,600		First day. Third day. Fifth day. Died.
34	М.		21,500		Autopsy.
3			20,400		
10 mos.			19,500		
9 mos.			17,600		
10 mos.			16,400 29,500		T. 103°, first day. Death, fifth day.
3			15,600		
3			15,400	55	
35	M.		14,700	68	Pleurisy also.
22	М.		14,400 19,400 13,200 19,300		January 25th. January 30th. February 2d. February 6th. Autopsy.

<sup>&</sup>lt;sup>1</sup> Cited by Rieder.

TABLE XXXIV.—Tuberculous Meningitis (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
6			14,000 18,000		First day. Fifth day.
6			13,900 21,400 17,400		First day. Fourth day, T. 102°. Tenth day.
3			13,100		
12			12,000		
8			11,500 11,900		First day. Fourth day.
35			10,800		
19			10,000 11,000		First day. Fourth day.
10 mos.			9,200		
22			8,200 13,300		First day. Seventh day.
30			8,100		
45	M.		8,000		
5			7,500		
40			7,000 10,000		First day. Fourth day.
24	F.	4,590,000	6,600	86	

In eighteen of my twenty-seven cases there was leucocytosis, sometimes very marked.

It seems therefore that pure tuberculous meningitis differs markedly from other pure tuberculous processes, in that it has in most cases a strong tendency to raise the leucocyte count. Osler's results point to the same conclusion. Ziemke has recently reported a case with 17,500 leucocytes per cubic millimetre. The red cells and hæmoglobin show, as a rule, but slight changes, as is so often found in other forms of tuberculosis. The absence of any increase

<sup>1 &</sup>quot;Text-book of Medicine," 3d edition.

<sup>&</sup>lt;sup>2</sup> Deut. med. Woch., April 8th, 1897.

in fibrin is, Türck thinks, of some diagnostic value in excluding other types of meningitis.

#### 3. Tuberculous Pericarditis.

In one case in which tubercle bacilli were repeatedly demonstrated in the fluid obtained by tapping the pericardial sac I found no leucocytosis. The counts in two others are shown in the accompanying table. I have not met with any other reports on the blood in this condition.

Case.	Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
$\frac{1}{2}$	19 48		4,728,000	6,200 7,000	60	

#### 4. Tuberculous Pleurisy.

No doubt a large proportion of all pleuritic effusions are tuberculous in origin; and, so far as I have seen, no high counts are recorded in cases proved by culture or inoculation to be tuberculous. The low leucocyte counts in most pleurisies (see above, p. 260) tend to show that they are tuberculous and not due to pyogenic organisms.

Pick mentions that he finds no leucocytosis in tuberculous pleurisy when uncomplicated by phthisis, but reports no actual counts.

#### 5. Glandular Tuberculosis.

In cases of so-called scrofulous glands, whether in children or adults, the blood shows no important changes except that in children the hæmoglobin may be considerably diminished.

### GLANDULAR TUBERCULOSIS.

No.	Age.	Sex.	White cells.	Per cent hæmoglobin.
1 2 3	20 28 7	F. M. F.	5,600 10,900 11,000	75 65

Leucocytosis is absent unless an abscess has been opened and infected. Whether or not tuberculosis of the abdominal or other internal lymph glands affects the blood, I am unable to say.

### 6. Genito-Urinary Tuberculosis.

Here the opportunities for a secondary pyogenic infection are so good that in well-marked cases we find the blood of septicæmia present. The following cases, all involving the bladder, kidney, and the external genitals, illustrate this point:

TABLE XXXV.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
50			20,100	58	
23		*	15,100		
6			15,000	62	T. B. in urine. Kidney operated.
30	M.	3,796,000	14,452	44	
23			12,600		Bladder.
31			11,000	55	Kidney.
40			10,400		
41	F.	3,588,000	10,400	55	
		3,000,000+	14,452		
22	F.		10,200		
27			10,100		
56			10,100		Testicle and lung.
32			9,700		
64			9,300		
35	F.	5,808,000	8,800	65	
8			8,500	70	
22	F.		8,400		
31	M.		7,600	57	
31	F.		6,900	60	
42	M.		7,000		December 18th.
			8,700		December 26th.
			8,300		January 11th.

#### SYPHILIS.

Reiss, in an article in the Archiv f. Dermatologie und Syphilis, 1895, Heft 1, says that the general constitutional influence of the poison of syphilis is best indicated by the condition of the blood. In one hundred cases he has arrived at the following conclusions regarding the

## Red Cells and Hæmoglobin.

During the time between the chancre and the secondary symptoms, the red cells are slightly decreased, but this is much more marked after the appearance of secondary symptoms and continues for a time even after treatment has begun. The hæmoglobin sinks steadily from the time of the primary lesion on, but is not especially affected by the eruption. Even under treatment the hæmoglobin

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never gets quite up to normal and prolonged mercurial treatment lowers it, although mercury has at first a beneficial effect on the hæmoglobin as well as on the other constituents of the blood.

Konried 'goes further into detail. According to him, in the first four to seven weeks after infection, the number of red cells remains normal, but the hæmoglobin begins to fall off, losing from ten to twenty per cent in that time. Afterward it sinks steadily until treatment is begun, the number of corpuscles also falling slightly.

Newmann and Konried, reporting in 1893 on two hundred cases, say that up to the time of the secondary symptoms from twenty-five to thirty per cent of hæmoglobin is generally lost, without much change in the red cells, which sink considerably in number after the outbreak of secondary lesions. Lezius likewise finds no diminution in the number of red cells until the outbreak of secondary lesions.

Ewing states: "With the outbreak of secondary symptoms the red cells begin to fall rapidly, reaching in untreated cases as low as 2,000,000 or less (Konried). In ten cases Wilbouchewitch found an average decrease of 229,000 cells daily. At the same time the hæmoglobin continues to diminish and may fall to 55–25 per cent. within a few weeks or months."

All these changes, like those about to be described, are apt to be more marked in women than in men. In cases going on to the secondary stage untreated, the hæmoglobin may sink to as low as twenty-five per cent. In the tertiary stages and in hereditary and so-called "constitutional syphilis" the red corpuscles are much more seriously affected, diminishing considerably in number as well as in weight and color. The hereditary syphilis of infancy may indeed produce fatal anæmia and very low counts are common, with large numbers of nucleated red cells and great deformities in shape and size.

The effect of mercurial treatment on the red cells is interesting. Gaillard 'found that the count of red cells increased during the first fourteen days, and the hæmoglobin during the first twenty-four days of treatment. After that time, if mercury was still given, the hæmoglobin and later the number of corpuscles began to decline.

Konried (loc. cit.) found the hæmoglobin to rise during the administration of the first twenty-five to thirty-five inunctions, after

<sup>&</sup>lt;sup>1</sup> International Dermatological Congress, 1892.

<sup>&</sup>lt;sup>2</sup> Wiener klin. Woch., 1893, No. 19.

<sup>&</sup>lt;sup>3</sup> Inaug. Dissert., Dorpat, 1889.
<sup>4</sup> Gaz. des Hôp., 1885, No. 74.

which it began to go down. This was in cases in which treatment was begun just after the onset of secondary symptoms. In the worst cases it sank even as low as forty-five per cent despite treatment, and this usually means a bad prognosis and severe tertiary symptoms to come. In one of my own cases the hæmoglobin was only thirty-seven per cent, though the red cells were 4,988,000 (color index, .37).

Ewing says: "In one the spleen was much enlarged and contained gummata, while the blood showed the lesion of grave secondary anæmia, with a tendency toward the microcytic type and a low hæmoglobin index. In other cases the abundant megalocytes with increased hæmoglobin closely resembled those of pernicious anæmia."

Potassic iodide increases the red cells and hæmoglobin, but has no special effect on the leucocytes.

Cases often show spontaneous improvement in their anæmia as well as in other symptoms.

Justus' in three hundred cases claims to have observed a peculiar reaction of the hæmoglobin in syphilis, which does not occur in any other disease, and which he considers of much diagnostic value.

According to him, if in cases in which secondary symptoms have not yet appeared, we test the hæmoglobin and then give an inunction or a subcutaneous injection of mercury, we find that within twenty-four hours a very marked fall in hæmoglobin has taken place (ten to twenty per cent), owing to the action of the mercury on the weakened corpuscles. This sudden fall is followed by a gradual rise until within a few days the coloring matter is at a point slightly higher than before the mercury was given. In diseases other than syphilis this sudden drop does not occur. After the advent of secondary symptoms the peculiar reaction to mercury does not occur. My own experience with the test is small. In nine cases of active syphilis I found it present. In three inactive cases and in thirty-five control cases of various other diseases it was absent. In a case of chlorosis the reaction was positive.

Brown and Dale<sup>2</sup> studied thirteen cases of syphilis, and concluded that the test is unreliable and of little practical value. In some of their cases the drop in hæmoglobin did not appear until several inunctions had been given.

<sup>&</sup>lt;sup>1</sup> Verhandl. d. 5 Cong. d. Deut. dermatolog. Gesellschaft, September, 1895.

<sup>&</sup>lt;sup>2</sup> Cincinnati Lancet-Clinic, March 24th, 1900.

Jones' examined thirty-five syphilities and eighteen control cases. Of seventeen cases of active syphilis thirteen gave positive results. Jones thinks the test of some value in diagnosis though by no means pathognomonic.

#### White Cells.

- 1. Here the changes are very characteristic. In the first stage the leucocytes are either normal or slightly increased, but the percentage of polymorphonuclear forms is almost always notably low, and that of the lymphocytes high. If mercury is given at this stage, the polymorphonuclear forms begin to increase toward normal, and the lymphocytes proportionately to decrease. [Mercury given to healthy persons has just the opposite effect, increasing the lymphocytes at the expense of the polymorphonuclear forms.] Iodide of potassium works exactly like mercury in this respect, increasing the polymorphonuclear leucocytes in syphilis, while it diminishes them in healthy persons.
- 2. As the eruption breaks out leucocytosis (12,750 and 16,800 in two of my cases) generally appears, the proportion of lymphocytes and of eosinophiles usually being increased. Engel describes a syphilitic child in whom the percentage of polymorphonuclear cells steadily rose as the child got worse. In such cases Engel considers these cells to be of prognostic importance. P. K. Brown has made a similar observation in bone tuberculosis. Treatment with mercury and potassium iodide tends to bring down the count of lymphocytes, while it raises the count of red cells; and among the white cells to increase the polymorphonuclear forms.

In the tertiary stages, with the severe anæmia which is often present, there occur occasionally leucocytosis, not uncommonly with small percentages of myelocytes, and a marked lymphocytosis. Müller<sup>2</sup> has described four cases of anæmia in syphilis so severe as to simulate pernicious anæmia very closely. In one the red cells sank to 720,000. Laache<sup>2</sup> mentions a similar case.

There are no constant changes in the blood plates. Specific gravity follows pretty closely the hæmoglobin percentage.

<sup>&</sup>lt;sup>1</sup> New York Med. Jour., April 7th, 1900.

<sup>&</sup>lt;sup>2</sup> Charité-Annalen, vol. xiv.

## Diagnostic Value.

Justus' reaction of syphilitic blood to mercury, if true, might be of great value in distinguishing early syphilis from various other causes of debility.

The occurrence in adults of leucocytosis with increased percentages of lymphocytes and of eosinophiles, is very suggestive of syphilis as against tuberculosis, typhoid, or malignant disease. In children, rickets and other diseases may give similar blood changes. The chief value of the blood examination, however, in syphilis is not for diagnosis but as a measure of the stage and severity of the infection. Low hæmoglobin and high percentages of the lymphocytes are characteristic of severe types. Leucocytosis usually means that the case has got beyond the primary stage, while in the tertiary stage the presence of myelocytes with a marked anæmia is of serious import.

Certain cases of this last type may closely resemble pernicious anæmia, from which, however, they are to be distinguished by their low color index, the frequent presence of leucocytosis, and the relative infrequency of megaloblasts as compared with the normoblasts, in case nucleated red cells are present.

TABLE XXXVI.—SYPHILIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1				24,000	70	Meningitis.
2	31			18,600		Tertiary. Liver?
3	27			16,500		Hemiplegia.
				12,700		Eleventh day.
4	25			15,900	80	Cerebral.
5	30			15,000		T. 100°, with iritis.
6	45			14,800		Cerebral.
7	40			13,200		Cerebral.
8	36			10,350	65	Cerebral.
9	48			9,700		Cerebral.
10	53			9,400	100	Cerebral.
11	29		5,880,000	8.640	52	Amyloid liver and spleen.
12	33			8,600		
13	51			8.400	100	Liver.
14	31			7,200		
15	49			6,500		
16	. 32			4,500		Testicle.

Dr. Thomas J. Yarrow kindly sends me a blood report of the following case, apparently of hereditary syphilis:

	Dec. 12th. 1898.	Dec. 20th.	Jan.4th, 1899.	Jan. 27th.	Remarks.
Red cells White cells	3,350,000 20,000				
Polynuclear Lymphocytes Eosinophiles	35.0g 44.6g 20.6g 60 per c.mm.	26.79 54.49 18.79	52. %	43.8%	The blood changes here reported coincided with the use of mercury and with the disappearance of the anæmia and of all symptoms.

### LEPROSY.

Winiarski (Petersburger medicinische Wochenschrift, 1892, p. 365) gives a careful study of seventeen cases of leprosy, and P. K. Brown' has watched sixteen cases. They find in young persons with mild cases no changes from the normal blood.

In severe cases, especially in old people, the anæmia may be severe (2,290,000 red cells with fifty-four per cent of hæmoglobin) and even comparable to pernicious anæmia (1,989,000 red cells with sixty-three per cent of hæmoglobin). In anæmic cases the color index is apt to be high, in one case it was 1.7 (1). Such severe types are associated with an increase of the average diameter of the red cells, which explains the high color index. The hæmoglobin was not relatively low in any case.

## Leucocytes.

No increase was present in any case. Four cases were subnormal. The percentage of lymphocytes, as in other debilitated conditions, is often high (forty-five to forty-seven per cent).

# Bacteriology of the Blood.

Brown has succeeded in demonstrating the leprosy bacillus in the blood of one-half of his cases. The bacilli appear for the most part within the leucocytes, and here they accumulate in large numbers. It is especially in the tubercular form of the disease that Brown has found them. He was unable to cultivate the bacillus.

Streker<sup>2</sup> has likewise found the bacillus in the blood of four cases.

<sup>&</sup>lt;sup>1</sup>San Francisco County Medical Society, July 13th, 1897.

<sup>&</sup>lt;sup>2</sup> Münch. med. Woch., 1897, Nos. 39, 40.

# PART IV.

## DISEASES OF SPECIAL ORGANS.

## CHAPTER VII.

### DISEASES OF THE DIGESTIVE APPARATUS.

#### 1. MOUTH.

In a case of thrush complicating chronic nephritis the following counts were recently recorded at the Massachusetts General Hospital: October 16th—red cells, 5,000,000; white cells, 16,200; hæmoglobin, 52 per cent. October 24th—white cells, 13,800; hæmoglobin, 55 per cent.

- 2. Œsophagus (see Malignant Disease, p. 370).
- 3. Stomach.

The conditions existing in the stomach may influence the blood profoundly in three ways:

- (a) They may be such as to prevent the normal absorption of nitrogenous material on which the blood, like all tissues, is absolutely dependent. Then the blood becomes starved. The extreme of this condition is the so-called "atrophy of the gastric tubules" which may produce a fatal anæmia. In lesser degrees the same process is at work in many forms of chronic dyspepsia, gastritis, or chronic starvation.
  - (b) They may lead to severe and repeated hemorrhages.
- (c) They may lead to an auto-intoxication which poisons the blood as well as other tissues.

On the other hand, it is probably through the influence of an altered blood serum on the duodenal mucous membranes that ulcer of the duodenum is a sequel to severe burns of the surface of the body.

For an account of the influence on the blood of digestion, ingestion of liquid, and starvation, see p. 97.

### DISEASES OF THE STOMACH.

### ANOREXIA NERVOSA.

From pure starvation the red cells may get as low as 900,000, as in the case mentioned by Martin. In the early stages the blood is normal. A recent hospital case showed 8,900 leucocytes with 87 per cent of hæmoglobin.

#### GASTRIC CANCER.

(See Malignant Disease, p. 380.)

#### GASTRIC ULCER.

## Red Cells and Hæmoglobin.

A severe anæmia is common. Out of the 51 cases in Table XXXVII., A, 42, 80 per cent, had less than 50 per cent of hæmoglobin, and of the 51 in which the red cells were counted, 17 had under 3,000,000 red cells per cubic millimetre. The average count of red cells at the time when treatment began was 3,372,000. There is no single disease, so far as I am aware, in which the red cells are so apt to be so low, except pernicious anæmia. Even cancer, as a rule, does not fall so low. This is due mostly, I think, to the frequency of hemorrhage from the ulcer; it is uncommon to see marked anæmia in patients who had never had a hemorrhage.

This anæmia is all the more striking when we remember that the frequent vomiting from which most patients suffer tends to concentrate the blood, *increase* the number of cells in a drop, and so to make the blood seem less anæmic than it really is. This tendency to concentration is probably effective in some of the cases observed especially by Oppenheimer, in which despite great pallor he found normal counts of red cells and hæmoglobin.

It is in such cases that the estimation of the dry residue of the blood serum would be of real value could it be made short and simple enough for clinical work. Grawitz, who is the prophet of this branch of blood examination, gives an interesting case illustrating this point.

A girl of twenty-five, suffering with peptic ulcer, and exceedingly pale, showed on counting the corpuscles 4,140,000 per cubic millimetre (no considerable reduction), and ninety per cent of hæmoglobin. A second count showed

<sup>&</sup>lt;sup>1</sup> Deut. med. Woch., 1889, No. 42,

4,340,000 corpuscles and ninety-one per cent of hæmoglobin. But the dry residue of the serum was reduced to three-fourths its normal amount. The serum suffers in anæmia as much as the corpuscles do. Any influence which deprived the serum of one-fourth of its normal solids (ædema being absent) must have really affected the corpuscles very much. Therefore the corpuscles must actually have been reduced to about 3,800,000, the reduction being masked by the concentration of the blood from vomiting. Lymph cannot have run into the vessels and diluted the serum, for (owing to the vomiting) the tide is all the other way. If then the serum is reduced a quarter the corpuscles must be so likewise. Unfortunately, to test the dry residue of the blood serum requires more time, skill, and apparatus than clinicians are apt to have. It is valuable whenever we wish to know whether or not an anæmia is being masked by concentration of the blood.

In severe cases the usual qualitative evidences of secondary anæmia (deformities, scanty normoblasts) are to be found.

TABLE XXXVII., A.—GASTRIC ULCER WITH HEMORRHAGE.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	32		4,864,000	22,000	75	Hemorrhage yesterday.
	20		3,968,000		45	Chlorosis.
3	52	F.	2,031,000		30	Hemorrhage and perforation.
4	27		1,860,000		20	Vomited small amount of blood.
$\begin{array}{c} 2\\3\\4\\5\end{array}$	23		3,480,000		43	V CAMPAGE SAMPAGE CONTRACTOR
6	35	M.	1,640,000		18	Bled four days ago. Diff. count
			_,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	,_,		500 cells:
		ĺ				Polynuclear, 74 per cent.
						Lymphocytes, 25 "
						Eosinophiles, .4 "
						Myelocytes, .6 "
						Megaloblasts, 4
						Normoblasts, 1
						Reds stain well.
						Many polychromatophilic.
			2,104,000	6,100	24	Sixth day. Diff. count 500 cells:
						Polynuclear, 60 per cent.
						Lymphocytes, 39 "
						Losinophnes, 1
						Megaloblasts, 0 Normoblasts, 1
			0 500 000	7,000	32	
			2,566,006	7,000	52	Thirteenth day. Diff. count 500 cells:
						Polynuclear, 58 per cent.
						Lymphocytes 39 "
						Eosinophiles, 3 "
						No nucleated reds.
			3,192,000		40	Twenty-first day.
			4,008,000		55	Thirty-second day.
7	29	F.	1,676,000		36	Large hemorrhage.
8	55	F.	3,664,000		45	
9	22		4,820,000		50	Perforation.
v	1	1	1 2,0,000	, 20,000	1	12 02202000

TABLE XXVII., A.—Gastric Ulcer with Hemorrhage (Continued).

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
10	48		1,448,000	13,700	10	Five days after perforation. Diff. count 500 cells: Polynuclear, 86 per cent. Lymphocytes, 13.6 " Eosinophiles, .4 "
11 12	42 32	F.	2,216,000 3,256,000 2,564,000	13,500 13,000 ?	32 35 20	Normoblasts, 1 November 11th. November 14th.
						Polynuclear, 83.2 per cent. S. lymphocytes, 10.4 " L. lymphocytes, 3.6 " Eosinophiles, 1.8 " Myelocytes, 1 " No nucleated reds; general tendency to small size, very few large forms; moderate poikilocytosis.
13	24		5,016,000	12,000	52	
14	29		3,644,000	11,400	35	Day after hemorrhage of O iij.
15	72		3,799,000	10,700	35	Autopsy.
16	35		3,024,000	10,200	55	January 2d.
			[3,392,000]	?	55	January 13th.
-4 100	40		[3,712,000]		45	February 5th.
17	40		3,868,000	9,900	50	
18	17		5,000,000	9,700	45	
19	27		[4,092,000]	9,300	40	
<b>2</b> 0	35		1,364,000	17,200	20	No autopsy.
	0.4		2,224,000	9,200	40	
21	24	F.	3,076,000	8,900	15	Bleeding.
22	20	• •	5,374,000	8,650	65	TT 1 1 1 1
23	37	::	3,267,000	8,500	30	Hemorrhage six days ago.
24	45		3,520,000	8,400	35	Dl-1 +1
$\frac{25}{26}$	$\begin{bmatrix} 37 \\ 30 \end{bmatrix}$	F.	4,188,000	8,100	35	Bled one month ago.
20	50	r.	$\begin{bmatrix} 3,432,000 \\ 4,222,000 \end{bmatrix}$	$7,820 \\ 10,600$	$\begin{array}{c} 45 \\ 75 \end{array}$	Hemorrhage previous day. Two weeks later.
			4,392,000	6,700	70	Three weeks later.
27	44		4,020,000	7,600	33	Three weeks later.
28	29		5,000,000	7,400	50	Slight hemorrhage.
29	26		1,888,000	7,400	19	Three days after hemorrhage:
					•	Polynuclear, 57 per cent. Lymphocytes, 41 " Eosinophiles, 2 "
						No nucleated reds; reds small but not much deformed.
30	22		2,984,000	7,200		October 3d.
			3,436,000	?	21	October 20th.
			3,612,000	?	34	November 1st.
31	24	F.	1,892,000	7,000	30	January 16th, after hemorrhage.
			2,304,000	?	27	January 22d.
			3,064,000	3,500	35	January 31st.
			3,920,000	?	48	February 10th.
00			4,680,000	?	55	February 28th.
32	20		3,340,000	7,000	45	

TABLE XXVII., A.—GASTRIC ULCER WITH HEMORRHAGE (Continued).

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
33	52		1,712,000	7,000	25	Five days after hemorrhage. Diff. count 300 cells: Polynuclear, 64 per cent.
						Lymphocytes, 35 " Eosinophiles, 1 "
0.4	00		4 000 000	w 000		Normoblasts, 1.
34	33		4,800,000	7,000	40	
35	26		3,280,000	6,800	30	
36	24		4,704,000	6,500	45	
37	30		2,544,000		30	
38	13		4,496,000		50	
39	48	F.	4,900,000	6,200	40	
40	23	F.	1,672,000	6,000	40	One pint of blood vomited yester-day; blood in stools; recovery.
41	30		3,920,000	6,000	30	Bled seven days ago.
42	24		3,196,000	5,900	15	
43	26	F.	2,968,000	5,300	45	Exclusive rectal feeding eight days.
44	19		4,432,000	5,000	58	Grippe and tonsillitis.
45	24		4,625,000	5,000	45	The state of the s
46	50	M.	1,554,000	4,800	25	Polynuclear, 74 per cent.
						Lymphocytes, 23 " Eosinophiles, 2 " Normoblasts. 2.
414	40	3.0	9 994 000	4 000	0=	
47	46	М.	3,324,000	4,800	35	Fell to 15 per cent after hemorrhage.
48	29		2,584,000	4,500	25	
49	38		3,616,000	4,300	35	Eleven days after profuse hemor- rhage.
50	29	F.	[1,972,000]	4,000	38	Recovery.
51	26		4,312,000	2,600	45	
0.1			_, 52.6, 500	,		

## TABLE XXVII., B.—GASTRIC ULCER WITHOUT HEMORRHAGE.

Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
17		5,380,000	12,100	60	
22		5,040,000	12,000	45	
21		5,000,000	11,800	70	
39	F.		11,100	68	
24		6,988,000	10,700	48	Vomiting.
19	F.	5,856,000	10,650	90	
40	F.	4,400,000	9,000	53	
23	F.		9,300	90	
22	F.		8,300	75	
30	F.		6,800	70	
25	F.		6,550	85	
35	F.		6,500	50	April 27th.
				45	June 6th.
47	F.		6,300	57	
38	F.		5,800	60	
19	F.		5,600	68	

TABLE XXXVII., B.—GASTRIC ULCER WITHOUT HEMORRHAGE (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
20 26 23 21	F F.	3,216,000 4,680,000 5,100,000	4,300 4,200	57 30 25 70	

### Hæmoglobin.

As a rule the color index is low. Only one examination in the cases of the Massachusetts General Hospital series showed an increased amount of hæmoglobin per corpuscle, and as this was not repeated or verified, it may have been a mistake. In most of the other examinations the color index was low.

Yet Osterspey records 1,900,000 red cells with 31 per cent of hæmoglobin (color index = .81); 3,296,000 with 70 per cent hæmoglobin (color index = 1.09); 4,048,000 with 84 per cent hæmoglobin (color index = 1.05). Such cases are certainly rare.

#### White Cells.

Leucocytosis is practically never seen except after hemorrhage and during digestion. When patients who have been fed for some time by the rectum are first given food by the mouth, the digestion leucocytosis may be very great, as in a case of the above series, in which the cells increased from 4,000 to 15,500! The presence of a leucocytosis, when the influence of bleeding and digestion is excluded, is against the diagnosis of ulcer of the stomach.

TABLE XXXVIII.—DUODENAL ULCER.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1 2	30 38	M. M.	3,776,000 1,700,000		50 17	
3	53		1,472,000	124,000	20	September 3d. Diff. count 500 cells: Polynuclear, 75 per cent. S. lymphocytes, 22.4 L. lymphocytes, 1.2 Eosinophiles, 1.2 Myelocytes, .2 Normoblasts, 1.
			1,876,000 2,148,000		$\begin{array}{c} 19 \\ 17 \end{array}$	September 10th. September 18th.
			2,440,000		21	September 24th.

TABLE XXXVIII.—DUODENAL ULCER (Continued).

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
4	47	М.	3,196,000 2,904,000 2,744,000 2,820,000 3,440,000 3,832,000 2,100,000 2,480,000 2,630,000	12,000 7,650 11,600 11,000 6,000	23 28 23 30 39 43 45 48 35  38 36	October 1st. October 8th. October 16th. October 23d. October 30th. November 6th. November 24th. December 15th. July 24th, much coffee grounds. July 29th (five days fasting). Four hours after meals. Constant feeding, July 30th. August 8th. August 21st, operation.

These figures are given simply to show that the blood in duodenal ulcer undergoes much the same changes as in gastric ulcer, and need no further comment.

#### ACUTE GASTRITIS AND DYSPEPSIA.

Acute gastritis or gastro-enteric attacks (Hayem's "embarras gastrique") do not affect the red cells or hæmoglobin, but are very often accompanied by leucocytosis (see Tables XXXIX., A and B).

TABLE XXXIX., A.—ACUTE GASTRO-ENTERITIS.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
31	M.	7,000,000	18,000		Temperature 104°. Well next day.
8	F.	4,800,000	17,800	50	Temperature 101°.
50	F.		15,100	70	
13	F.	5, 184, 000	15,000	85	Well next day.
28	M.		14,400		September 17th, temperature 103°.
			12,800		September 18th.
			9,100		September 21st, temperature normal
30	F.	4,860,000	14,200	80	Well in three days.
20	M.		12,000	67	
36	F.		11,600	68	
23	F.	6,244,000	11,600	86	Well in two days.
17	F.	4,600,000	11,000	70	
29	F.		11,000		Temperature 101°.
70	F.	4,632,000	10,000	90	
37	М.	4,186,000	9,200	68	
28	M.		6,900	90	Temperature 102°.
23	F.	3,860,000	6,400	65	
57	F.		6,000		Temperature 101°.
23	F.	5, 144, 000	5,400	95	
32	F.		5,200	50	Temperature 100°.

Where this is the case, it may help us to exclude typhoid fever, which has no leucocytosis. Even a twenty-four hours' dyspeptic attack may increase the leucocytes notably, as in Cases 1 and 2 in Table XXXIX., A, and the presence of such an increase need not make us suspect anything behind the dyspepsia. It is probably to be classed as a toxic leucocytosis due to absorption of morbid products from stomach or intestine. Fibrin may be increased during the period of leucocytosis.

_			Thin Hilling, D. Distribut May Charlettis.									
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin,	Remarks.						
1	24	M.	6,280,000	22,700		Gastralgia; constipation; whole						
2	27	F.	4,750,000	12,800 14,000	74	belly tender. Three days later; well in a week. At mealtime, 11,200; four hours later, 12,150.						
3	26	F.	4,920,000	11,000	55	Dyspepsia.						
3 4 5 6 7	23	M.		11,000		Acute gastritis.						
5			5,016,000	8,924	86							
6	37	М.		7,326	77	Chronic gastric catarrh.						
7	30	F.	3,678,000	7,000	75	Nervous dyspepsia.						
8	41	M.	4, 524, 000	6,000	68	Before meal, November 1st, 6,000; November 2d, 6,300.  After meal, November 1st, 6,800; November 2d, 7,400.						
9	49	F.	4,200,000	4,000	80	Chronic gastritis.						
10	18	F.	5,016,000	3,200	45	Dyspepsia.						
11	60	M.	3,504,000	2,800	50	Chronic gastritis.						

TABLE XXXIX., B.—DYSPEPSIA AND GASTRITIS.

#### CHRONIC GASTRITIS.

## (See Cases 6, 9, and 11, Table XXXIX., B.)

Here the conditions are different and we never find an increase of the white cells, but often a decrease due to malnutrition. Digestion may produce no leucocytosis, or the increase may be very slight and late in appearing (four to five hours after a meal instead of two to three hours). It was present in nine out of twelve cases in our series.

Anæmia is very often present and may be extreme. It is believed by very high authorities that a *pernicious* anæmia may be caused by chronic gastritis with atrophy of the gastric tubules. The writer has never had the good fortune to see such cases.

The practical points about the blood of chronic gastritis are:

(a) The not infrequently severe anæmia.

(b) The not infrequent absence of digestion leucocytosis as in gastric cancer, from which therefore the absence of digestion leucocytosis does not distinguish it.

The presence of a leucocytosis militates against the diagnosis of chronic gastric catarrh, and, if hemorrhage is excluded, points toward cancer.

## HYPERACIDITY AND HYPERSECRETION.

The leucocytes average higher in these conditions than in chronic gastritis or dyspepsia with normal or decreased secretions (see Table XL.). Otherwise the blood is not remarkable.

TABLE XL.—HYPERACIDITY AND HYPERSECRETION.

_						
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	Adult.	M.	5,024,000	12,300	82	
1 2 3	30	F.	5,768,000	10,800	82	Chronic gastritis.
3	40	M.	5,300,000	10,000	85	Slight digestion leucocytosis:
						12,270 before meal, 14,300 three hours later.
4	. 40	M.	3,340,000	7,780	70	Dilated stomach; no digestion leucocytosis.
5 6	28	F.	4,016,000	5,994	76	100000 10010.
6	57	M.	4, 160, 000		34	Lead poisoning and dilated
						stomach.

#### DILATED STOMACH.

No.	Age.	Sex.	Red cells.	White cells.	Per cent. hæmo- globin.	Remarks.
1 2 3 4 5	22 51 47 30 64	M. M. F.	6,216,000 4,184,000 4,720,000 5,000,000 5,264,000	9,600 8,000		Nervous dyspepsia. Movable kidney.

### DILATED STOMACH.

In many cases proteid absorption is so faulty that the blood is severely starved, but the anamia may be concealed by the concentration of the blood brought about by the constant vomiting of large amounts of fluid. Kussmaul has shown that patients often vomit more fluid than they ingest, and it is obvious what must be the drain of this process on the fluids of the blood and all other tissues.

Digestion leucocytosis is often absent, as in cancer or chronic gastritis.

#### CORROSIVE GASTRITIS.

The blood was examined in a case of this kind in 1895 at the Massachusetts General Hospital with the following result: Red cells, 3,792,000; white cells, 32,500; hæmoglobin, fifty-three per cent.

### DISEASES OF THE INTESTINE.

INFLUENCE OF SALINE CATHARTICS ON THE BLOOD.

Hay' gives the following figures, showing the effect of sulphate of sodium in concentrating the blood: Healthy man of thirty-three, 3:35 p.m. Red corpuscles, 5,025,000; given 85 c.c. of a concentrated solution of sulphate of sodium in water; thirty-five minutes later blood count showed red corpuscles, 6,540,000; sixty-five minutes later blood count showed red corpuscles, 6,790,000; four hours later blood count showed red corpuscles, 4,930,000. Evidently much fluid was drawn out of the blood-vessels, and then within four hours the tissues had supplied the loss and the blood had returned to its normal density.

Hay also showed that dilute solutions of the same salt had far less effect in concentrating the blood. Further he demonstrated that if the blood is *already concentrated* when the saline is given, no purgative effect follows.

Grawitz confirms these results; he found also that common salt still further concentrates the blood (hence its production of thirst), and considers that (as this concentration accelerates *coagulation*) the household use of salt water as a remedy to stop hemorrhage is well founded.

#### ACUTE ENTERITIS.

Practically the great majority of cases of acute enteritis are part of a gastro-enteric attack, and in Table XXXIX. (see p. 298) the two have been lumped together. What was said of that table (p. 299) need not be here repeated. Besides the slight leucocytosis there mentioned, we may find in cases in which the stools are very watery, a temporary concentration of the blood with increased specific

 $^{\rm I}$  Hay: "The Action of Saline Cathartics." Journal of Anatomy and Physiology, 1882, p. 430.

gravity and red corpuscles. In infants the lymphocytes are apt to be increased at the expense of all the other varieties. Eosinophiles may be absent. Thus in a case of subacute colitis following an attack of influenza pneumonia, Wochnert found ninety-seven per cent of lymphocytes in a total count of 14,000 white cells. The other three per cent. were polynuclear.

TABLE XLI.—ENTERITIS, COLITIS, AND DYSENTERY.

******						
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	45	M	3,840,000	17,000	50	Chronic dysentery. August 26th.
	40	MI.	0,040,000	14,300		September 3d.
				7,700		" 5th, dysentery ceased.
				8,800		" 20th.
2	25	F.		17,000		Chronic entero-colitis.
3	Adult.		3,624,000			Chronic entero-colitis.
4	Adult.		4, 320, 000			777
-	Addit.	211.	2,732,000			
			4, 488, 000			Three weeks later; much im-
			4,400,000	0.000		proved.
5	39	F.	6,776,000	8,900	100	Acute febrile dysentery; bloody
U	00	r.	0, 110,000	0,500	100	movements every hour.
ß	3	F.	4,800,000	7,900		Ulcerative colitis.
17	Adult.	M	4, 100, 000		72	Chronic enteritis.
S.	27	M.	4,872,000		12	" diarrhœa and tetany.
6 7 8 9	20	M.	5,008,000		39	" diarrhœa and tetany.
10	26	M.	4,900,000	5,300	80	Bloody stools ten days.
11	65	M.		5,200	80	Catarrhal entero-colitis.
12	40	F.	2,996,000	5,000	37	Chronic colitis.
13	27	F.	4,500,000	5,000	70	Diarrhea.
14	34	F.	3,920,000	4,200	71	Chronic colitis.
14	04	Γ.	3, 320, 000	4,200	11	Chromic contas.
-						

#### CHRONIC DIARRHŒA.

## (See Table XLI.)

In acute diarrhea the other tissues respond to meet the loss of fluid sustained by the blood, and the blood is soon normal again. But when this process goes on long, the body becomes so wasted that the blood must share in the starvation and the albuminoids are drained out of it, leaving it watery and poor in corpuscles. A patient of Grawitz after years of chronic dysentery had but 1,880,000 red cells per cubic millimetre, while the serum had twice the normal amount of water, and half the normal amount of solids. I have seen the count fall as low as 1,928,000 in a case of prolonged colitis, with final recovery. In another case the red cells reached

<sup>&</sup>lt;sup>1</sup> Journal of the American Medical Association, February 2d, 1901.

no lower than 2,440,000, but the hæmoglobin was only ten per cent. A differential count of this man's blood showed the following:

	Per cent.
Polymorphonuclear neutrophiles	. 66.3
Lymphocytes (small)	. 24.9
Lymphocytes (large)	. 6.0
Eosinophiles	. 1.4
Myelocytes	. 1.4

While counting 400 leucocytes I saw 8 normoblasts and 5 megaloblasts. The total leucocyte count was 9,800 per cubic millimetre.

Cases 1, 3, 4, 12, and 14 of the series in Table XLI. show similar conditions. The hæmoglobin, however, usually suffers most, and the color index is low.

Leucocytosis is rare, but does occasionally occur, possibly owing to some complication or auto-intoxication.

TABLE XLII.—INTESTINAL OBSTRUCTION.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	1 mo.			34,200		Intussusception; died.
2				22,100		Twenty-first day; hernia.
				21,700		Twenty-second day; autopsy.
3			3,120,000	20,800		Cancer.
4	52	M.	5,568,000	18,860		May 6th; cancer.
				18,800		May 17th; cancer.
5	Adult.	M.		14,666		No fæces three days.
						No urine two days.
				12,400		One day later, no fæces; urine drawn by catheter.
				4,100		Three days later, bowels moved six times.
6	50	F.		12,200		Cancer of uterus.
7	35	M.	3,504,000	12,000		Chronic obstruction with hemorrhage.
8	21	M.	5,150,000	12,000		Obstruction (by a band).
9	56	F.	4,440,000	12,000	52	Cancer.
10	57	F.	4,272,000	11,000	75	Cancer.
11	Adult.	M.	5,800,000	6,800		
12	72	M.	4,850,000	6,000		
13	29			6,000		Obstruction by band; operated.
14	58		4,480,000	5,800	90	Cancer.
15	Adult.	M.	5,200,000	4,000		
16	"	M.	5,540,000	4,000		

Cholera is discussed on p. 226.

For appendicitis see Abscess, p. 240.

#### INTESTINAL OBSTRUCTION.

Bloodgood's conclusions are as follows:

In the first forty-eight hours obstruction, if without gangrene or peritonitis, gives a leucocyte count of only 6,000 to 16,000. The higher the count and the shorter the duration the greater the probability of gangrene. If there is a count of over 20,000 within the first twenty-four hours, the chances are that gangrene is present. After the third day, if the leucocyte count remains high, the prognosis is good.

Any pathological condition whatever which produces obstruction is followed in a few hours by a rise in the leucocyte count.

The only point brought out by Table XLII. is that the white cells may be increased, especially when the obstruction is cancerous. Hence the blood count cannot be relied on to help us in the diagnosis between obstruction and peritonitis. It is more likely that the examination of the amount of fibrin will be useful, as it is said to be increased in peritonitis and not in obstruction.

## DISEASES OF THE LIVER.

#### CATARRHAL JAUNDICE.

The serum is colored yellow or greenish-yellow and contains bile pigments in solution. It has been asserted that jaundice can be recognized here before it shows in the skin or urine. In mild cases, i.e., when some bile goes to the intestine and the obstruction is not of long standing, the blood is practically normal, as the cases in Table XLIII. show. Only one of these cases shows any leucocytosis,

Age.	Sex.	Red cells.	white cells.	Per cent hæmo- globin.	F	emarks.
47			14,700		Seven weeks.	Catarrhal (?).
21	. M.		10,500	81		(1)
26			10,400	60		
44	M.		10,200			
41			10,000	62		
25	F.	4,310,000	10,000	77		
			10,000	90		
			8,000			
30	F.		9,600	68		
34	1		9,200			

TABLE XLIII.—CATARRHAL JAUNDICE.

TABLE XLIII.—CATARRHAL JAUNDICE (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
42	M.	2,896,000	8,775	47	Alcoholic gastritis.
40			8,200	75	
40			8,100		
$\frac{40}{28}$			8,000 8,000		
37			7,500		
30	1		7.500		
26	M.		7,500		
21	M.	4,800,000	7,500	65	
30	M.		7,400	64	
30	M.	4.040.000	7,300		
53	M.	4,240,000	6,793	79	·
24 44	• •		6,300 $6,200$		Obstruction.
29	m.		6.200	82	Obstruction.
	M.	4,996,000	6,000	78	
24		2,000,000	6,000	78	
25			5,400	30	Polynuclear, 78 per cent.
					Lymphocytes, 19 "
					Eosinophiles, 1 "
					Intyerocytes, #
					$\frac{1\frac{1}{4}(?)}{\text{Reds pale, deformed.}}$
					1 normoblast.
32			5,300		March 16th.
		5,600,000	4,700	75	
35	M.	4,350,000	4,900	85	
44		3,168,000	4,800	85	
29	F.		4,200	85	
10	13		9,600		
19	F.		4,000		

and the red cells and hæmoglobin have not suffered except in the alcoholic case in which other causes for anæmia were present. This is contrary to the observations of Grawitz, who found constantly leucocytosis, but agrees with those of v. Limbeck and Hayem, who never found any increase of leucocytes or any other changes in the blood count. Coagulation in this or any other type of obstructive jaundice may be very slow, but this is especially apt to be true in gall-stone cases even if no jaundice is present. Coagulation may be increased to eleven minutes (Osler) and patients may bleed to death during operation on gall stones. The amount of fibrin is normal. Von Limbeck noticed an increased resistance of the red cells to the influence of distilled water and dilute saline solutions which in normal blood dissolve the hæmoglobin. He noticed also that the size of the red corpuscles was greater than normal, their

volume in a given amount of blood being seventy-seven to eighty-one per cent (i.e., they take up seventy-seven to eighty-one per cent of the room occupied by the drop), while the normal is about forty-four per cent. This was in cases with only from 4,000,000 to 5,200,000 red cells per cubic millimetre, so that it was evidently due not to an overcrowding of the drop with red cells, but to a true increase of size in the individual cells. The same fact has been attested from a different point of view by the investigations of v. Noorden, who found the solid residue increased, and of Hammer-schlag; and Grawitz has noted an increase in the specific gravity of the whole blood, though that of the serum remained normal. Normal red corpuscles put into the serum of icteric patients increase their diameter considerably, so that apparently the serum is responsible for the change.

## Qualitative Changes.

Grawitz noted in severe cases that crenation took place much more rapidly than usual in freshly drawn blood, and that the rouleaux formation did not take place. This latter point was also noticed by Hofmeier in icterus of the new-born. Silbermann noticed in the same disease great deformities in the size and shape of the cells. In severe febrile icterus Weintraud noted in the red cells the white spots and streaks with active (molecular) movements described by Maragliano (see p. 83) as endoglobular degenerative changes.

## Summary.

Normal blood, except for increased size of the red cells and some degenerative changes in severe cases.

## Diagnostic Value.

The constant presence of leucocytosis excludes an uncomplicated "catarrhal" jaundice, and points to the probability of malignant disease or inflammation (cholangitis, abscess). Syphilis and cirrhosis of the liver might show the same condition of the blood unless the characteristics of syphilitic blood were very marked (see p. 286). From a severe cholæmia the absence of any marked anæmia distinguishes a purely catarrhal case. (For the changes in cholæmia see p. 312).

<sup>&</sup>lt;sup>1</sup> "Die Gelbsucht der Neugeborenen," Stuttgart, 1882.

<sup>&</sup>lt;sup>2</sup> "Die Gelbsucht der Neugeborenen." Arch. f. Kinderheilk., 1887, p. 401.

#### CIRRHOSIS OF THE LIVER.

## 1. Ordinary (Atrophic) Cirrhosis Without Jaundice.

In the early stages (according to Hayem) neither the red cells nor the hæmoglobin fall considerably. Most other observers (perhaps thinking chiefly of the later stages) report marked anæmia. Wlajew¹ counted from 3,000,000 to 4,000,000 red cells; v. Limbeck had a case with only 1,500,000. He noted that the count might be increased after a tapping in cases with ascites, owing to the concentration of the blood from the rapid refilling of the belly with serum. Grawitz, on the other hand, noticed precisely the opposite effect in a patient whose blood before tapping had been concentrated by cyanosis, the heart's action being embarrassed by the ascites. After tapping, when the heart's action had become easier and stronger, the cyanosis disappeared and the blood count fell from 4,700,000 to 4,300,000. In v. Limbeck's case it rose from 4,680,000 to 5,160,000. The moral is that we should draw no inferences from the count of red cells soon after a tapping.

The thirty-seven cases in Table XLIV., A., were all advanced and their red cells averaged only 3,580,000 + per cubic millimetre. They steadily decrease as the disease progresses, one case getting as low as 1,300,000; but the anæmia may be concealed by eyanosis and concentration.

## Qualitative Changes.

Hayem noticed a curious stickiness of the red corpuscles, a great tendency to adhere to each other. Von Limbeck looked for it, but could never find it. Hayem and Maragliano noticed degenerative endoglobular changes in the red cells ("état cribriforme").

MARKE	VIIV	A Crapmonro	LIVER WITHOUT	T
TABLE	X 1 . I V	A — CIPPHOTIC	LIVER WITHOUT	TOTAL LABORATOR IN THE

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
58		4,504,000	29,300	60	T., 100°. Delirium tremens.
35	.,	908,000	18,500 26,000	20	Fourth day. Intestinal hemorrhage. Diff. count
					500 cells: Polynuclear, 85 per cent. Lymphocytes, 14 " Eosinophiles, .8 " Myelocytes, .2 " Normoblasts, 10 Megaloblasts, 0
		1,732,000	19,800	25	Seventh day. Diff. count 500 cells: Polynuclear, 88 per cent.

<sup>&</sup>lt;sup>1</sup>Ref. in Petersburger med. Woch., 1894, No. 43.

TABLE XLIV., A.—CIRRHOTIC LIVER WITHOUT JAUNDICE (Continued).

		1131 (1) 111			million dictibles (continued).
Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
53 51 53 54 63 41 60 47 40 46 63 48 48 53 50 50 50 50 51 50 51 50 50 50 50 50 50 50 50 50 50 50 50 50	F	2,456,000 3,098,000 2,950,000 4,300,000 4,300,000 4,992,000 2,120,000 1,300,000 2,350,000 2,450,000 4,500,000 3,100,000 3,100,000 3,100,000 3,144,000	## White cells.    16,900	hæmo-	Remarks.  Lymphocytes, 10 per cent. Eosinophiles, 1 " Myelocytes, 1 " Normoblasts, 2 Fourteenth day. Thirtieth day. First day. Uræmic symptoms. Eleventh day. Autopsy. Hæmoptysis. Autopsy. Recent hemorrhage. Tapped; 328 ounces. With mitral disease. Liver enlarged. Ascites. Autopsy.  Recent hemorrhage. March 15th. April 8th. April 18th. April 18th. April 29th. May 10th. May 12th. June 10th. June 16th. Liver enlarged.  Tapped; 144 ounces.
48 38 45	F.	4,888,000 5,720,000 2,830,000	6,100 5,700 5,200	65 65 46 40	Differential normal count.
14 54 56	 М. М.	2,830,000 3,480,000 4,680,000	5,500 5,500 5,400 5,000	55 64 48	Liver atrophic, July 12th.
42	M.	4,312,000 2,920,000	4,000 $4,500$ $13,400$ $15,300$	62 56 	July 25th. October 30th. November 7th, during digestion. November 11th, during digestion.
53 54 63 50 52	M. F. M. M. M.	3,844,000 3,568,000 3,440,000	3,800 3,300 3,000 2,400 2,400	72 65 50 50	

## Hæmoglobin.

Usually the color index is low; the average was .66 in the ten Massachusetts General Hospital cases.

#### White Cells.

Except after recent hemorrhage none of our cases showed any leucocytosis and the average count was 7,240, some cases having notably low figures (2,400, 3,000, 4,500).

Hayem's results agree with this. Von Limbeck makes no definite statement on this point. Rosenstein and Wlajew found leucocytosis, the latter 12,000 to 17,000. Possibly their cases include the forms of cirrhosis with jaundice in which (see Table XLIV., B) the white cells are more often increased.

The forms of hypertrophic cirrhosis without jaundice (fatty infiltrated liver) are here classed with the atrophic cases whose blood has just been described.

TABLE XLIV., B.—CIRRHOTIC LIVER WITH JAUNDICE.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
29		3,700,000	20,000	30	Toxic symptoms. Delirious.
42	M.	1,024,000	19,600	36	Autopsy.
38	M.	3,400,000	19,500	50	
51		3,960,000	19,200	47	Hæmoptysis. Delirious. Death.
32			18,200	65	T. 102°-104°. Liver enlarged.
36			15,600		
45	M.		14,000	65	Liver enlarged.
28			12,400	65	Ascites.
57			12,200	63	
35		5,016,000	12,000		Liver enlarged.
54			9,300		Ascites.
33	••	3,740,000	8,700	50	Differential count 400 cells: Polynuclear, 87 per cent. Lymphocytes, 12 " Eosinophiles, 1 " Normoblasts, 1
			19,200		Twentieth day. High fever, toxic symptoms.
			22,000		Twenty-fourth day. High fever, toxic symptoms. Autopsy.
36	M.	2,064,000	4,300	50	Jaundice only transient.
50	M.	2,904,000	2,400	54	Autopsy (hypertrophic cirrhosis).
57	F.			••	Adult cells, 83 per cent.; young cells, 17 per cent.

Fifteen cases.

### 2. Hypertrophic Cirrhosis with Jaundice.

### Red Cells.

True (biliary) hypertrophic cirrhosis with jaundice has according to Hayem an intense anæmia in many cases. In others it has no more effect on the blood than ordinary atrophic cirrhosis. The six cases in Table XLIV., B, averaged a little lower in the count of white cells than the ten atrophic cases, 3,200,000 as contrasted with 3,580,000.

## Hæmoglobin.

In a single case of this variety of cirrhosis Hayem found in four successive blood examinations a color index of more than 1. His counts are as follows:

Date.	Red cells.	White cells.	Per cent hæmoglobin,	Color index.
January 9th	1,599,600		41	1.27
" 11th		21,803	50	1.39
" 12th		18,082	50	1.46
" 15th		15,500	53	1.40

Dried specimens showed an increased average diameter of the cells as in pernicious anemia. The patient died January 15th, and the autopsy confirmed the diagnosis of hypertrophic cirrhosis.

The observations of v. Limbeck of the increased volume of the red cells in *jaundice* may perhaps be another example of the condition here noted by Hayem. The presence of bile in the blood makes all hæmoglobin estimations unsatisfactory.

Only one of our six cases showed this same condition—Case 13 in Table XLIV., B. The corpuscles numbered 2,064,000, or forty per cent, and the hæmoglobin fifty per cent, a color index of 1.25. This case was jaundiced at the time of the examination.

I have seen no confirmation of Hayem's observations by any other writer.

#### White Cells.

Leucocytosis is commoner in this than in the other variety of cirrhosis. Hanot and Mennier found from 9,000 to 21,800 leucocytes per cubic millimetre in five cases of hypertrophic cirrhosis, and an average of 6,600 in ordinary cirrhosis. Leucocytosis was present in four of the six cases of the Massachusetts General Hospital series, the average of all six being 9,000.

## Diagnostic Value.

The blood of either form of cirrhosis has no diagnostic value, so far as I know, except to exclude abscess and hydatids. If no leucocytosis is present, abscess and hydatid cyst can usually be excluded.

#### HYDATID CYST OF THE LIVER.

The only observations which I have met with are those of Hayem and Neusser. Hayem states that the blood shows leucocytosis and increased fibrin. Neusser considers that the increase of eosinophiles, which he finds in hydatids, serves to distinguish them from hydronephrosis, dilated gall bladder, etc.

"Auche in one case ruled out the diagnosis of hypertrophic cirrhosis from the absence of an excess of leucocytes."

In a single case I recorded white cells 34,000.

#### ECHINOCOCCUS CYST.

Age.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
31	• 3,664,000	8,650	48	Iceland.

#### ACUTE YELLOW ATROPHY OF THE LIVER.

Grawitz records a case with 5,150,000 red cells and 16,000 white cells.

A single case with autopsy was studied at the Massachusetts General Hospital in 1894, the blood showing 5,520,000 red cells, 12,000 white cells, and sixty per cent of hæmoglobin.

Ewing reports three cases with leucocytosis, 15,000 to 21,000. "The absence of rouleaux and early crenation mentioned by Grawitz were not noted."

#### PHOSPHORUS POISONING.

Taussig, v. Jaksch, Badt, and v. Limbeck note an *increase* in the normal number of red cells per cubic millimetre. Taussig found 8,650,000 per cubic millimetre; Badt, 6,400,000, 6,500,000,

<sup>&</sup>lt;sup>1</sup> Arch. f. experiment. Path. und Pharm., vol. xxx. <sup>3</sup> Dissert., Berlin, 1891.

<sup>&</sup>lt;sup>2</sup> Deut. med. Woch., 1893, p. 10. <sup>4</sup> Loc. cit., p. 34.

and 6,800,000 in three successive cases; v. Limbeck, 6,500,000 and 7,900,000. That this increase is not due to concentration of the blood through vomiting of liquid is proved by v. Limbeck's last case, in which no vomiting whatever took place.

The count usually falls to normal within a few days. All these changes were verified in thirty-three cases at the Stockholm Hospital in 1892 (see Stockholm Hospital reports for 1892).

The white cells in v. Limbeck's second case were increased to 12,500. In v. Jaksch's five cases the counts were 58,750, 48,000, 8,000, 4,070, and 3,400.

#### CHOLÆMIA.

When jaundice is intense and long standing, as in complete obstruction of the bile ducts by gall stones or tumors, the blood is weakened very notably, and hæmoglobin and the count of corpuscles fall steadily. Very little is to be learned upon the subject from the literature, but the qualitative changes mentioned under catarrhal jaundice are much more marked, and leucocytosis is apt to be present. I have studied the blood in a case of fatal chronic jaundice without fever and for which at autopsy no cause was found. The leucocytes ranged between 12,000 and 14,000.

#### GALL STONES.

Netter' and Sittmann<sup>2</sup> have found pyogenic organisms in cultures from the blood of patients with gall stones, as have also Gilbert and Girode.<sup>3</sup> The *slow coagulation* is of great surgical importance.

"The pneumococcus of Frankel and streptococcus pyogenes were obtained from the blood in one case each, both complicated by hepatic abscess, by Canon and by Zaucarol."

Of the 22 cases of this disease examined at the Massachusetts General Hospital 2 were complicated with cholangitis (see Table XLV., A). Excluding these 2, leucocytosis was present in only 4 of 20 cases. The red cells were low in 2 cases (2,800,000 and 3,900,000).

The absence of leucocytosis helps us to distinguish the disease from peritonitis and appendicitis, and excludes suppurative cholangitis.

<sup>&</sup>lt;sup>1</sup> Progrès Médical, 1886, No. 46.

<sup>&</sup>lt;sup>2</sup> Deut. Arch. f. klin. Med., 1894, p. 323.

<sup>&</sup>lt;sup>2</sup> La Semaine Méd., 1890, No. 58.

## GALL STONES.

TABLE XLV., A.—GALL STONES.

Age.	Sex.	Red cells.	White cells.	Per cent	Remarks.
			COIIS.	globin.	itemarks.
25			28,200		
39	F.	4,768,000	24,000		Cholangitis also.
30	F.	4,820,000	20,000		Cholangitis. Autopsy.
63	F.	4,610,000	18,800		Cholangino, Lintopoj.
29	M.		16,200		December 16th.
			13,200		December 18th.
			10,000		December 21st.
60			14,300		First day. Pus in gall bladder.
			20,700		Fourth day.
40	T3	4 500 000	15,000		Fifth day. Operation.
40 60	F. F.	4,520,000	13,000	770	100 59
60	F.		12,500	72 70	Temp. 100.5°.
25			$\begin{vmatrix} 11,500 \\ 11,600 \end{vmatrix}$	10	
46		4,176,000	11,400	45	
63		1,110,000	11,300	40	Obstructive jaundice.
39		4,168,000	10,500	65	No pain.
37			10,300		In colic.
40	M.		10,250		
60		4,336,000	10,200	45	
55			10,200		In pain.
		4,448,000	10,000	58	Sixth day. Operation.
49	F.		10,000	90	Jaundice.
40	• •	• • • • • • •	9,900	05	
47 56			9,800	85	
41			$9,700 \\ 9,400$	90	No pain.
32	• • •		9,400		No pain for two days. T. 100°.
33			9,400		Colic.
00			5,200		Colic.
32			9,200		No colic.
45	F.		9,200	100	
38	F.		8,900	60	Distended gall bladder.
25	F.	5,072,000	8,800		Jaundice.
40			8,300		No pain.
46			8,200		Colic.
27	7/5	0.000.000	8,200		Day after colic.
22	M. F.	3,288,000	8,000	• •	Jaundice.
$\begin{array}{c} 25 \\ 54 \end{array}$		4,900,000	8,000 7,800		Between attacks.
50 50			7,700	• •	Deep jaundice.
37			7,600	60	Deep Jaundice.
54	F.		7,600	80	
40			7,400	60	August 25th.
			3,700		August 27th.
		4,336,000	11,500	50	August 31st.
		0.000.000	15,100		September 6th.
40		3,636,000	10,600	40	September 7th.
48	E.	9.944.000	7,400		
29 57	F. F.	2,844,000	7,400	85	
37	F.		$7,400 \\ 7,300$		October 1st.
91	I.		8,200		October 1st.
48			6,700		Between attacks.
	, , ,		-,		

TABLE XLV., A.-—GALL STONES (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
58	M.		6,000	64	
57	F.		5,400	68	
51	F.		5,300	63	
28			5,200		In colic, proved at operation.
24	M.	4,320,000	4,000		Recurrent pain and jaundice.

#### CHOLANGITIS.

Here the leucocytosis is well marked whenever the inflammation has got beyond the catarrhal stage (see Table XLV., B), and helps us to exclude simple impacted gall stone, with or without colic. Cancer may or may not produce leucocytosis, but does not usually increase the fibrin network; it is said by Hayem that cholangitis does increase it.

TABLE XLV., B.—CHOLANGITIS.

No.	Age.	Sex.	Red cells.	White cells.	Remarks.
1 2		F. F.	4,800,000 6,400,000	50,000 30,000	Suppurative cholangitis.
3		F.	4,960,000	22,000	T
4 5	21 65	M. M.	4,976,000	14,800 14,186	Jaundice and cholæmia. Gall-stones: chills.
5				11,000	October 20th. Operation October 22d. Abscess of liver.
7	28	M.	6,640,000	9,000	Catarrhal.
8	34	F.	$\begin{bmatrix} 5,592,000 \\ 4,770,000 \end{bmatrix}$	6,800 4,400	Catarrhal.

TABLE XLV., C.—CHOLECYSTITIS.

Age.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.		
48		23,000 15,500		First day. Infectious. Third day.		
$\frac{36}{32}$		22,600 15,600	60 73	Suppurative. Gall stones.		
25		12,200	60	Gan stones.		
58 50		10,700 8,300	80			
44	3,602,000	46,300 6,600	50	Ten days later. Suppurative. Typhoid.		

The blood does not differ from that of cholangitis with suppuration. From cancer it may often be distinguished by the absence of increased fibrin network in cancer, while it is always increased in suppurations.

#### ABSCESS OF THE LIVER.

In all but one of the cases seen by the writer (see Table XLVI.) the leucocytosis has been very marked. I have never been able to account for its absence in that case.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin,	Remarks.
20	M.	4,533,000	33,200 48,000		January 11th. January 14th. Operation.
15 60	F. F.	3,750,000 4,460,000	26,800 18,000		Operation.
28 33	M. F.		12,600	• •	November 3d.
99	г.		11,000 17,500		November 4th, 11 A.M.
			19,200 20,600		November 4th, 2 P.M. November 5th, 10 A.M. Operation;
26	M.	2,664,000	10,200 12,000	33	autopsy. October 19th.
			15,000		October 20th. October 21st. October 25th, au-
51	F.	3,440,000	9,600		topsy; streptococci.

TABLE XLVI.—ABSCESS OF THE LIVER.

#### CANCER OF THE LIVER.

(See Malignant Disease, p. 385.)

#### GUMMA OF THE LIVER.

Von Jaksch in a single case found red cells, 2,756,000; white cells, 6,100.

#### DISEASES OF THE PANCREAS.

#### HEMORRHAGIC PANCREATITIS.

Opie records a leucocytosis of 19,600 in a case operated by Bloodgood (Johns Hopkins Bulletin, January, 1901).

At the Massachusetts General Hospital we have had a case in which the following are recorded:—22,800, 9,200, counts of white cells.

#### ACUTE HEMORRHAGIC PANCREATITIS.

Age.	White cells.	Per cent hæmoglobin.		_
26. 50.		100	Fourth day.	

#### DISEASES AFFECTING THE HEART.

#### PERICARDITIS.

(See Inflammation of Serous Membranes, p. 265.)

#### ENDOCARDITIS.

In many cases of acute endocarditis the blood shows no changes. In others, whatever alterations there may be are covered up by those involved in the *rheumatic* arthritis associated with the endocarditis.

#### ULCERATIVE ENDOCARDITIS.

In ulcerative or malignant endocarditis, we may find the signs of a pyogenic infection (see p. 231). Sometimes pyogenic cocci can be cultivated from the blood, and if present may be of the greatest value in a diagnosis always difficult to make.

Grawitz goes so far as to say that in doubtful cases repeated negative results of cultures from the blood make it unlikely that ulcerative endocarditis is present.

Sittmann' considers that important help may be given as to the position of the primary focus of infection by the nature of the organism present in blood cultures—i.e., the pneumococcus pointing to the lung, the colon bacillus to the intestine, etc.

#### Red Cells.

As in all forms of septicæmia marked anæmia rapidly develops, more rapidly probably than in any other disease. The hæmoglobin loses about equally with the corpuscles, according to most observers—that is, the blood destruction is so rapid that the red cells do not get thin before they die, as is usually the case, but are cut off in the prime of health.

Further evidence of rapid blood destruction is seen in the hæmoglobinæmia often present.

Roscher (*loc. cit.*) records counts of 4,400,000 and 2,750,000, both fatal cases. In one case seen by the writer the count was 3,792,000 with fifty-eight per cent. of hæmoglobin.

White Corpuscles.

Rieder reports a single case showing these variations:

			Temperature.	White cells,
January	2d,	1891		17,000
44	3d,	1891	 99°	13,700
66	8th,	1891	 103°	15,500
44	10th,	1891	 101.5°	18,000
"	12th,	1891	 101.5°	21,300
44	18th,	1891	 101°	18,800
66	22d,	1891	 104.5°	13,000
T7 1	44.9			

February 11th, the patient died.

Pée found leucocytosis. Roscher in two cases found: Case I.: 8,800 leucocytes; the patient died in two days. Case II.: 16,800 and 12,000. Krebs in one case found: October 27th, 15,500; October 28th, 44,200; the patient died the same day.

"Grawitz reported 168,000 leucocytes in one case."

Twenty-two cases were counted at the Massachusetts General Hospital with the following results:

TABLE XLVII.—ULCERATIVE ENDOCARDITIS.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
21			34,300		
			39,200		Third day.
			27,000		Tenth day.
			47,600		Seventeenth day. Died twenty- first. No autopsy.
			30,100		May 27th.
			15,800		May 30th.
			18,100		June 17th.
8 yrs.		4,216,000	26,100	50	November 20th.
11 mos.			27,000		November 23d. Aortic stenosis.
			27,500		November 27th. Mitral insuf-
			27,400		
			25,000		December 9th. ficiency.
			16,600		December 22d.
			25,700		May 22d.
			27,840		May 24th.
			18,100		May 26th.
			22,000		May 28th.
29			22,800		
18			22,700		
			20,400		Autopsy.
27			20,300	75	(Six months' fever.)
29			19,100		Autopsy.
35			18,900		Pneumonia, January 28th, 1899.
			31,300		February 4th, 1900. No signs but
					a systolic murmur and chills.
			20,400		February 11th.

TABLE XLVII.—ULCERATIVE ENDOCARDITIS (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
			20,900 40,400		February 15th. February 21st.
			31,000		February 23d.
			$\begin{vmatrix} 37,400 \\ 63,700 \end{vmatrix}$		February 25th. March 1st.
			37,150		March 4th.
			,		March 7th. Autopsy. Malignant endocarditis.
63			18,800 8,600		April 7th. T. 102°. Pneumonia. April 10th. Pneumonia gone. T. 99°.
			18,300		April 14th, 8 a.m. T. 104.5°. Aortic and mitral.
			29,200		6 P.M.
			35,800		April 15th, 7 A.M. Culture of blood (14th). Pneumococci.
35		2,718,000	15,200	25	Polynuclear, 86 per cent. Lymphocytes, 14 " Eosinophiles, 0 "
3 yrs. 11 mos.			13,500		No autopsy.
44		3,996,000	13,400 18,000	55	October 18th. October 22d.
			12,600		January 13th.
			14,500		January 14th.
			$20,400 \\ 24,000$		January 16th. January 18th; died.
21		5,330,000	11,300 9,000	45	January 8th.
			11,700	42	Pulmonary embolism.
			18,700	50	March 15th.
		2 702 000	13,900	48 58	April 6th. No autopsy.
• • • •	• •	3,792,000	$10,000 \\ 8,900$	55	Autopsy.
28			7,900		Hyperplastic.
32			7,600		Autopsy.
23		3,884,000	5,200	45	December 15th.
					Polynuclear, 91.2 per cent. Lymphocytes, 6.7 "
					Eosinophiles, 2.1 "
			11,900		December 27th.
		4,272,000	10 100	50	December 31st.
			$10,100 \\ 8,800$		January 7th. January 14th.
		3,560,000	0,000		January 15th.
			21,300	45	January 26th.
			15,100		January 30th.
		2,852,000	6,200 $9,800$	35	February 24th. March 8th. No autopsy.
38		3,652,000	3,000	50	Polynuclear, 77.0 per cent.
00		2,00.2,000	5,000		Lymphocytes, 22.5 "
					Eosinophiles, .5 "
					No nucleated reds. Autopsy.

Practically the same are the counts in the following cases of apparently "benign" endocarditis with fever and rapidly shifting murmurs, the seventh complicating chorea in a boy of thirteen.

TABLE XLVIII.—"BENIGN" ENDOCARDITIS.

Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
56	F.		50,100		November 24th.
			35,800		November 27th.
			36,600		November 30th.
			22,800		December 7th.
4			29,600		Twenty-first. T. 102°.
			28,500		Twenty-second. T. 98°.
- 1			19,600		Twenty-fifth.
28			24,800		Twenty-fourth.
			11,700		Twenty-fifth.
11		4,728,000	24,500	55	First day.
			17,700		Seventh day.
			14,000	55	Fourteenth day.
			15,100		
			10,800	55	
			10,100	34	
27	٠٠.		24,000	80	First day.
			16,000		Fourth day.
			13,600		Fifth day.
29			21,320		Pregnancy four months.
13	$\mathbf{M}$ .	• • • • • • • • •	20,600	62	May 26th. T. 102°-104°.
			17,900		May 29th.
1			18,700	• •	May 31st.
			16,800	• •	June 3d.
			21,200	• •	June 4th.
			27,400	• •	June 8th.
			$22,700 \\ 24,200$		June 11th.
			21,900		June 13th. June 15th.
			26,100	• •	June 17th.
			26,800	• •	June 19th.
			17,400	• •	June 23d.
			28,700		June 26th.
			21,200		July 2d (outdoors).
			21,300		July 4th. Left the hospital July
			~1,500		19th.
17			19,800		December 16th. Mitral insuffi-
1.			20,000		ciency. Renal colic.
			19,200		December 20th.
26			12,000		Salpingitis.

# Diagnostic Value.

<sup>(</sup>a) Blood cultures should never be omitted in cases of suspected malignant endocarditis. When positive they are of great value.

(b) In excluding typhoid, malaria, and miliary tubercle the presence of leucocytosis is important. I saw within a few months a case in

which several consultants had made the diagnosis of typhoid, but in which the presence of marked and persistent leucocytosis and the absence of a typhoid serum reaction convinced me that the case was one of ulcerative endocarditis. This has since been verified.

#### MYOCARDITIS.

Whenever stasis and disturbance of the circulation result from weakness of the heart wall, blood changes identical with those described under Valvular Heart Disease are present. Otherwise the blood is normal.

Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
51			30,000	75	No autopsy.
54			13,200	68	Mitral disease with broken compensation.
62			12,900		1
53		4,944,000		45	Broken compensation. Chronic bronchitis.
60			10,700		•
62			10,700		Mitral insufficiency.
75			8,800		Syncope. Chronic interstitial nephritis.
58			8,300	63	Progressive muscular atrophy. Arthritis deformans.
55			7.400		
68			7,200		Chronic interstitial.
67			6,700		Chronic interstitial.

TABLE XLIX.—MYOCARDITIS.

#### VALVULAR HEART DISEASE.

Grawitz divides valvular heart disease into three stages with corresponding blood conditions:

- 1. Stage of full compensation: blood normal.
- 2. Stage of *acute* failure of compensation: blood diluted (Oertel's "plethora serosa").
- 3. Stage of chronic stasis and cyanosis: blood concentrated for the most part; at times diluted as well.
  - 1. A valvular lesion per se has no effect on the blood.
- 2. When compensation fails and blood pressure is lowered, we find (especially in the venous blood) that the fluid from the surrounding lymph spaces has made its way into the vessels and diluted the blood. The specific gravity falls, red cells and hæmoglobin are lower than before, while the white cells are unaltered, and the plasma is shown to be more watery than before, as well as of increased

quantity per cubic millimetre. All these changes are less marked in capillary blood, and hence are rarely observed.

3. If the heart adjust itself partially to the increased work it has to do, and to the chronic passive congestion of the internal organs and at the periphery, the blood is concentrated, probably in part by transudations into serous cavities and lymph spaces, and in part by the increased excretion of moisture by the lungs. The specific gravity and the number of red cells are increased, especially in the capillaries, and to a less extent in the venous blood (the conditions being just the reverse of those in acute heart failure, stage No. 2). This is the condition usually found in heart disease with chronic venous stasis (passive congestion).

But this concentrated condition of the blood may be offset from time to time by fresh weakening of the heart and lessening of blood pressure, and the combination of the two conditions may result in a normal blood count.

The condition of concentrated peripheral blood with the count of red cells above normal is that most commonly seen in chronic heart disease with stasis.

Von Limbeck finds that aortic lesions are more apt to show a normal or diminished blood count, while mitral disease is more apt to be accompanied by the temporary dilutions and long-standing concentration above described. He does not explain the cause of this, and it does not coincide with my cases. One of his patients with double mitral lesion showed a decrease of 1,170,000 red cells (from 7,500,000 to 6,330,000) after exertion. When the patient was quiet, the lesion was compensated; on exertion compensation temporarily failed, blood pressure was lowered, and the blood diluted.

Sadler' found considerable anæmia in three out of four cases of aortic disease, while only two of seven patients with mitral lesions showed anæmia.

Schneider's results were similar in that he found the red cells normal in the aortic cases and increased in the mitral ones.

Hayem found anæmia most common in aortic regurgitation, especially in young people.

In the Massachusetts General Hospital records there have been a strikingly large number of cases of mitral disease associated with severe anæmia (see cases 2, 10, 14, and 88 of Table L.). The counts

<sup>&</sup>lt;sup>1</sup> Loc. cit., p. 33.

<sup>&</sup>lt;sup>2</sup> Inaug. Dissert., Berlin, 1888.

of red cells in twenty cases average 3,400,000, and nucleated red cells were found in three cases. These were all of them *supposed* to be chronic cases without any active endocarditis, septic or benign, and were for the most part afebrile. In view of the marked anæmia and leucocytosis, however, I am in doubt whether the endocarditis was really as dormant as the temperature and the absence of chills or embolism would suggest.

In the cases of aortic disease due to arterio-sclerosis, there was no considerable anæmia or leucocytosis.

# White Corpuscles.

Almost all writers whom I have consulted agree that the leucocytes are normal unless some complication occurs. Yet in a large number of the Massachusetts General Hospital cases the leucocytes were steadily *increased*, while the red cells were diminished (see Table L.) This leucocytosis cannot be explained as the result of stasis, since it is rare in aortic disease or in myocarditis, despite stasis, and is found chiefly in mitral cases. That stasis plays a part in the blood counts of congenital heart disease seems evident from the cases next to be mentioned, in which the red cells are increased only about forty per cent., while the white are often one hundred per cent. more numerous than normal.

The apparently normal count of red cells in some of our cases may have been due to the covering up of an anæmic or diluted condition of the blood by concentration, the resultant of the two forces being an apparently normal count.

In the 91 cases of mitral disease tabulated on pages 323–325, there are 51, or 56 per cent, showing leucocytosis of more than 11,000, and 32 with over 16,000 leucocytosis. In some of the cases there was pulmonary infarction or nephritis as a complication, and these lesions may have influenced the count.

The polynuclear cells are proportionately increased. In explanation of the anemia and leucocytosis of mitral disease and the lack of these phenomena in aortic disease, I conjecture that mitral disease is rarely long dormant, and that the "failures of compensation," for which my cases sought the hospital, were associated with or due to fresh vegetative or thrombotic processes on the valves.

Œdema and diuresis have in themselves little or no constant effect upon the blood, as a recent observation of Petrowsky's has demonstrated.

#### CONGENITAL HEART DISEASE.

In the cyanosis accompanying this affection very high blood counts are reported. Gibson found:

Case.	Red cells.	White cells.	Per cent hæmoglobin.
1 2		12,000 12,000	110 92

Carmichael reports, red cells, 8,100,000, white cells, 16,000, in a single case, and Toeniessen counted 8,820,000 and 7,540,000 in two similar cases. In one case entirely without evidence of any stasis I counted 8,431,000 red cells per cubic millimetre. Townsend has collected 30 such cases with counts ranging from 6,000,000 to 9,000,000. How such cases are to be explained I do not know; the ordinary explanation of concentration of the blood will not hold in cases in which no stasis or lack of compensation exists, yet the skin is blue and the blood counts are enormous.

There is no doubt that the peripheral capillaries always contain more corpuscles per cubic millimetre than do the veins. Numerous reports from various observers agree upon this. Whether this is on account of the loss of water by perspiration and consequent drain of blood from the skin capillaries is uncertain, but in congenital heart disease both capillary and venous blood is overcrowded with corpuscles and the explanation is difficult. Hayem in a case of this sort reports 7,000,000 red cells with a decrease in the average diameter.

TABLE L.—MITRAL VALVE DISEASE AND ITS COMPLICATIONS.

				cent globin.	LE	sions.		
No. Age.	Sex.	Red cells	White cells.	Per contraction has been been been been been been been bee	Mitral.	Aortic.	Tri- cuspid.	Remarks.
1 26 2 39		3,448,000	44,000 43,150	70 55	M. M.	 A.		Died same day. July 5th. Polynuclear, 71.4; lympho-
	• • •	2,596,000	8,800	43	M.	Α.		cytes, 27; myelocytes, 6; masts, 4. July 9th. July 10th, autopsy. Fresh and old endocarditis.
3 30			32,000	62	M. Ruptured			
4 44	• • •	4,480,000	20,400 27,000	40	comp. M.	••		Temp., 100°. Fifth day. Purpuric spots.

Table L.—Mitral Valve Disease and Its Complications (Continued).

-									
					Per cent hæmoglobin.	LE	sions.		
			Red cells	White cells.	er ce			Tri-	Remarks.
No.	Age.	Sex			hæ	Mitral.	Aortic.	cus	
5	32			30,000 19,000		М.			First day with infarcts. Temp., 102°.
	31 36			23,000 22,600	78	M. M. Double.	A.	т.	Third day. Died on fifth. No fever.
				22,600 24,600					Fourth day. Sixth day.
8	23			19,000 22,400 22,100		М.		T.	Seventeenth day. Pulmonary infarction.
9 10	8		2,624,000	22,100	35	M. M.			With nephritis. Polynuclear, 88; lym- phocytes, 12; eosinophiles, 0; 2 normoblasts. (Count 500.) Died.
11	19			20,800	65	M. Stenosis.			
12	25		3,756,000	11,700 20,700	35	M.	A. Double.		Four days later. Temp., 96°. April 10th.
			3,680,000	13,000	35	••••	**		April 20th. Temp., 104.6°. (Count 500.) Polynuclear, 86.6 per cent.; small lymphocytes, 8.6; large lymphocytes,
13	50			20,500	75	M.			1 normoblast. No autopsy.  Dilated and hypertrophied with pul-
14	16	F.	2,672,000	20,500	42	M.	A.		monary infarct. Acute nephritis.
16	40			20,400 20,000	70	M. M. Double.			Cerebral embolism.
				15,000 10,400					Third day. Seventh day.
17 18	45 39		3,244,000	19,900 19,700	35 55	M. M.		::	No autopsy. With acute nephritis.
20	38	М.	3,648,000	19,600 19,300	45	Stenosis. M. M. Stenosis.			Pulmonary infarction; bloody pleurisy. Albumin one-fourth per cent.
21 22 23	22 35 35			19,000 19,000 18,000	72	M. M. M.		::	With nephritis. Broken compensation.
24	9		4,160,000	18.000	60 55	M.		::	First day. Temp., 197°. Thirteenth day.
25 26	54			1.30.000	65 65 80	M. M.			Twenty-second day. Hydrothorax. Temp. 98°. Died.
27 28	30 40			18,000 17,900 17,100 16,800	65 65	M. M.			No fever. Temp., 101°+.
29 30	5		3,808,000	16,400	45	M. M.			Pulmonary infarction. Temp., 99.5°.
31	34			16,000 11,000		М.	A.	::	First day. Seventh day. Temp., 101°.
				21,000	68				Fourteenth day.
32	56			9,400 $16,000$ $15,400$	60	M. M.	A. A.		Thirty-fifth day. Temp., 99-100°.
34	30		3,920,000 3,840,000	8,600	38 43	M.	A.		First day. Temp., 99°. Eleventh day.
35	38			15,000 14,100	65	М.		T.	Temp., 97°.
36	27			14,000	100	M.	A.	т.	First day. Third day. With diffuse perhapitis
-38	158			14,000 14,000	::	M. M. M.	A.	::	With diffuse nephritis. Temp., 98°, with myocarditis. Temp., 98°, with nephritis. Temp., 98°.
40 41	58		3,814,000	13,400	50 55	M. M. M.	A.		Temp., 98°.
42	119		3,820,000 4,876,000	13,100	55	M. M.	A.		Temp. usually subnormal.

TABLE L.—MITRAL VALVE DISEASE AND ITS COMPLICATIONS (Continued).

					cent globin.	LE	SIONS.		
No.	Age.	Sex.	Red cells	White cells.	Per cent hæmoglobin	Mitral.	Aortic.	Tri- cuspid.	Remarks.
	21 28 52			12,800	60	M. M.	A. A.		
46 47	52 41			12,800 12,800 12,500 12,100 11,400	80	M. M.	A.		
48 49	25 46		4,480,000 4,500,000	11,400 11,200	45 40	M. M.	A. A.		Temp., 98°. With angina.
50	21			11,200	52	M. Double.			
52	168			11,200 11,000	65	M. M.			Temp., 98°.
54	34			11,000	65	M. M.			Temp., 98°.
56	45 54		.,	10,600	72 77	M. M.	A.		Asthma.
58	43 40			9,900		M. M. M.	Ä.		Broken compensation. Temp. subnormal.
60 61	19 27 25			9,900 9,900 9,800	70	M. M. M.	A.		Temp., 98°.
62	40 28			9,600 9,600		M. M.	A.		Temp., 98°. Broken compensation.
64	20	• • •		9,500	70	M. Double.			Temp., 100°.
$\begin{array}{c} 65 \\ 66 \end{array}$	$\frac{39}{54}$			$9,400 \\ 9,400$	65	M. M.		::	Broken compensation. Broken compensation.
			5,360,000	9,200 9,200	100	M. M.	Α.		
69	33			9,000	72	М.			December 14th.
71	61		6,452,000 4,953,000	8,900	95 48	M.			December 21st.  Broken compensation. No autopsy.
73	46			8,800 8,800 8,600	60	M. M. M.	Α.	• •	Temp., 98°.
75	46 40			8,500 8,400	::	M. M.	 		Fever. Gonorrhoea (?). Temp., 97°. Temp., 96°. Temp., 98°.
77 78	40 38			8,200 8,000		M. M.	 A.		Temp., 98°.
19	OU			7,900 7,900		M. M.			Broken compensation. Temp., 97°.
81	50			7,800		Stenosis. M.			Temp., 97°.
8%	44	• • •	4,040,000	7,500	55	M. Double.			
84	40			7,300 7,000	::	M. M.			
86	28 32			6,800 6,600	::	M. M.			
87	50 30		1,600,000	6,000 6,000	iò	Double. M. M.	Α.		First day Polynuclean & & lympha
00	50	• • •	1,000,000	0,000	10	M.	Α.	••	cytes, 38; eosinophiles, 4; megalo- blasts, 1; normoblasts, 8; reds pale, large, deformed.
			1,536,000	4,200	10	••••	••		First day. Polynuclear, 61.6; lymphocytes, 38; eosinophiles, 4; megaloblasts, 1; normoblasts, 8; reds pale, large, deformed.  Seventh day. Polynuclear, 67; lymphocytes, 32; eosinophiles, 1; megaloblasts, 4; normoblasts, 7. Large oval forms.
			1,728,000 1,720,000	5,000	15 12½	••••	::		Fifteenth day. Twentieth day. Polynuclear, 71; lymphocytes, 27; eosinophiles, 2; megaloblasts, 1.
89	<b>5</b> 9		1,840,000	5,200 6,000	18	м.	 A.		Twenty-seventh day.
901	40			5,800 4,900	70	M. M.	Ä.		Temp., 98°.

_					
Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
42			31,000	50	
52			12,000	60	First day. Temp., 101°.
			20,000		Third day. Temp., 102°.
			26,000		Sixth day. Temp., 102°.
			25,000		Eighth day. Temp., 101°.
			30,000		Fourteenth day. Temp., 101°.
			21,600		Twentieth day. Temp., 99.3°.
~ 0					Twenty-seventh day. Autopsy.
					Angina.
24		5,024,000	6,800	60	
			6,000		With chronic diffuse nephritis.
24			5,000		•
78			3,200		Temp., 98°.
22		4,400,000		45	-
56 24 37 24 78 22		5,024,000	5,000	60	Twentieth day. Temp., 99 Twenty-seventh day. Auto Angina. With chronic diffuse nephrit

TABLE LI.—AORTIC VALVE DISEASE.

The most important practical deduction from these data is that a blood count in a patient suffering from poorly compensated heart disease has no value in determining whether or not anæmia is present. The actual number of corpuscles in the body is not measured by the number contained in a drop of peripheral blood, since anæmia may be effectually masked by concentration or simulated by dilution.

This holds good equally for any condition involving general stasis and cyanosis either from embarrassment of the heart's action or otherwise (for instance, pneumonia in certain stage, emphysema, displacement of the heart by serous effusions, or tumors), or local stasis of the part from which blood is taken. Penzoldt' noted that in old hemiplegic cases the blood from the affected side contained more corpuscles than that from the sound side, and the writer has noticed the same thing in a variety of vasomotor affections involving local asphyxia.

#### ANEURISM.

As a rule I have found the blood entirely normal, but in the following case it might have thrown light on the diagnosis. A patient was recently admitted to the Massachusetts General Hospital with an acute affection of the chest, supposed to be pneumonia in spite of the slightness of the fever and the irregularity of the physical signs. At autopsy a ruptured aortic aneurism was found. The blood count had showed 3,324,000 red cells, 20,800 white, and 33 per cent Berliner klin. Woch., 1881, p. 457.

hæmoglobin. The low percentage of hæmoglobin and red cells was really inconsistent with an acute pneumonia in a man previously well, and might have hinted strongly toward the correct diagnosis had attention been directed more carefully to the blood. After gelatine injections, leucocytosis always appears.

#### DISEASES OF THE KIDNEYS.

Many factors other than the disease itself may influence the blood of nephritic cases. For instance, in scarlatinal nephritis the long-standing leucocytosis is probably due largely to the scarlatinal poison, rather than to the nephritis. The occurrence of large quantities of blood in the urine has the same influence as any other hemorrhage upon the blood.

*Œdema* as such has apparently very little effect upon the blood, but the *loss of albumin* in the urine tells both on the corpuscles and on the serum, thinning both with consequent lowering of the specific gravity of the blood.

#### ACUTE NEPHRITIS.

## 1. Red Cells and Hæmoglobin.

Whether largely from the loss of blood from the kidneys or from other causes, the red cells are often much diminished, but the hæmoglobin suffers still more.

#### HÆMOGLOBINURIA.

Age.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
31	3,428,000	14,300	40	With esophageal symptoms.

Laache reports an average loss of nineteen per cent of the red cells and twenty-six per cent of their coloring matter.

Hayem found no considerable loss of red cells unless the urine was hemorrhagic. The following cases illustrate his results:

Case I.—Acute nephritis, ending in recovery.

	Red cells.
March 17th, 1882	3,069,000
March 31st, 1882	2,759,000
April 7th, 1882	2,821,000
May 1st, 1882, albuminuria ceased.	
May 17th, 1882	3,038,000
May 31st, 1882	3,689,000

Case II.—Acute (puerperal) nephritis; recovery.

		Red cells.
April	6th, 1881	2,945,000
66	9th, 1881	2,976,000
66	12th, 1881, no albumin in urine.	
66	13th, 1881	3,137,500
66	20th, 1881	3,310,000
CASE III	.—Nephritis (chronic?) with hæmaturi	a.
Red c	ells	2.821.000

(It should be noted that Hayem's counts are low on the average, and the instrument used by him was not very reliable.)

Grawitz in acute nephritis records 3,400,000 red cells at the beginning of the third week, and 3,100,000 ten days later.

Koblank¹ counted 5,168,700 in a case of acute nephritis with œdema.

Sadler (*loc. cit.*) in six cases of acute nephritis found in two cases 3,590,000 and 2,262,000 red cells; in the other four practically normal counts.

TABLE LIL.-ACUTE NEPHRITIS.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
18 mos.			36,000		Parenchymatous.
56	F.		22,000		Temperature, 102.5°.
			14,000		Sixth day.
			11,900		Ninth day, temperature falling.
			12,200		Nineteenth day.
54			16,850	70	
24		4,020,000	14,000	60	
11	F.	4,068,000	14,000	52	
45	M.	3,532,000	13,200	43	
40		4,880,000	12,700	65	
40			12,600	75	
13	F.		12,000		
11			11,800	70	
23	M.		11,700	50	
35			11,500	85	
24	F.		11,100	85	
		5,228,000	10,800	50	
33	M.	3,904,000	9,300	50	Purpura also.
22	M.	4,300,000	8,300	48	*
22	M.		7,600	60	
44	F.		7,500	65	

<sup>&</sup>lt;sup>1</sup> Inaug. Dissert., Berlin, 1889.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
37 25 55	M.	4,080,000	6,800 6,600 6,200	78 40	Parenchymatous.
20 20 22	 М. F.	5,000,000	6,200 6,000 5,400	58	Parenchymatous. Acute parenchymatous.
20 39		4,090,000 3,752,000	5,100 5,100	55 65	Acute parenchymatous.

TABLE LII.—Acute Nephritis (Continued).

In none of the few cases examined at the Massachusetts General Hospital were the red cells much diminished, but in two cases the hæmoglobin was very low, the color index being .62 in one and .61 in the other.

The blood plates are much increased (Hayem) and fibrin is slightly increased.

#### 2. White Cells.

Leucocytosis is usually stated to be the rule, lasting often for weeks at a time and gradually diminishing in convalescence.

Hayem gives counts of 14,973, 12,400, 15,000, and 13,000.

Koblank (*loc. cit.*) and Grawitz each in a single case found *nor-mal* counts (7,300 and 5,600).

Sadler found an increase in only one of his six cases, and then the highest point reached was 13,312.

Of the twenty-six cases of Table LII., leucocytosis was present in seventeen, in one of which it was followed for three weeks and still persisted; but it is my own belief that the leucocytosis of acute nephritis is due either to loss of blood by the kidney or to uræmia. When these conditions have been absent I have not found any leucocytosis.

# CHRONIC DIFFUSE AND CHRONIC PARENCHYMATOUS NEPHRITIS.

#### Red Cells.

In advanced stages the counts may run very low, but more often it is chiefly the hæmoglobin that suffers through the drain of albuminoids from the blood into the urine. Hayem gives the following figures:

Case I.—Chronic parenchymatous nephritis.

	Red cells.	Per cent hæmoglobin.
June 20th	4,309,000	43
July 4th	4,216,000	44
October 18th	2,945,000	34
Case II.—Same diagnosis.		

		Red cells.	Per cent hæmoglobin.
March	6th	2,619,500	36
46	8th	2,836,500	36
46	23d	2,464,500	27

Koblank (loc. cit.) in the same disease found 3,291,700 red cells in a single case with much ædema.

Reinert found 4,050,000 with 50 per cent of hæmoglobin and 3,604,000 with 62 per cent of hæmoglobin.

Sadler:		
	Red cells.	
Case	4,120,000	
	(2,405,000—November 19th	h.
66		
	$ \begin{pmatrix} 2,405,000{-}\text{November 19t} \\ 1,100,000{-}\text{January 14th.} \\ 1,500,000{-}\text{January 17th.} \end{pmatrix} $	
66	4,300,000	
66	4,300,000 4,300,000	
66	3,737,500—June 28th. 3,593,700—July 3d. 2,187,500—August 15th.	
	2.187.500—August 15th.	
	( 2 200 000 Tuly 7th	
66	3,200,000—July 7th. 3,257,000—July 22d. 3,137,000—August 21st.	
	9,207,000—July 220.	
	(5,151,000—August 21st.	

Grawitz in an acute exacerbation of a chronic parenchymatous nephritis found 1,928,000 red cells.

The Massachusetts General Hospital cases show a considerable anæmia in nine out of the thirty-six, or one-quarter of the series. Great concentration is probably the cause of the very high counts in certain cases. The majority of cases are not far from normal so far as the number of red cells goes, and the hæmoglobin is also very little diminished.

#### CHRONIC NEPHRITIS.

		ed cel		Cases.
Between	1,000,000	and	2,000,000	. 1
66	2,000,000	66	3,000,000	2
66	3,000,000	66	4,000,000	11
66	4,000,000	.66	5,000,000	13
44	5,000,000	66	6,000,000	6
66	6,000,000	66	7,000,000	3
	Color ind	lex a	verages about .7.	36

#### White Cells.

Hayem records 25,000, 19,000, 13,000, 10,000, and 6,000, and concludes that the counts vary much not only in different cases, but in the same case at short intervals.

Koblank found 14,700 in a single case.

Sadler in one case found 6,300 in November and 16,000 in the following January; 12,000 in another case; 8,800, 7,700, and 1,916 in others.

TABLE LIII., A.—COUNTS IN CHRONIC NEPHRITIS WITH URÆMIA.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
32	F.		44,000		Eclampsia.
35			25,000		Coma first day.
			9,000		Clear twelfth day.
29	F.		22,600		
21		4,080,000	20,400		
29			18,900	80	Temperature, 102.5°.
29	M.		18,650		Polynuclear, 83%.
35	F.		18,600	٠.	Coma five weeks after miscarriage.
35			18,000		November 21st, arterio-sclerosis.
			15,800		November 23d.
		4,184,000	18,100	60	December 2d.
		2,320,000	16,800	18	January 4th.
18			17,800	81	
11	· · ·	5,236,000	17,450	52	Eclampsia.
49	F.		16,800		C1 1 7100
33			16,300	::	Chronic diffuse.
36		4,650,000	16,300	58	Polynuclear, 86.7%.
	{				Lymphocytes, 13.3.
25		0.004.000	10000		No nucleated reds or deformity.
25		3,604,000	16,200	50	Chronic diffuse.
20	F.		15,800		Differential count normal.
32			15,800		Chronic diffuse. Eclampsia.
53			15,000		
00	3.5		13,200		
38	M. M.		15,000		
45			15,000	70	Chronic diffuse. Died in one month.
$\frac{35}{37}$	w		$14,300 \\ 14,200$	10	Chronic diffuse. Died in one month.
15	M. F.		13,800		
25	M.		13,400		
23 13		2,360,000	12,800	44	Polynuclear, 77%.
19		2,500,000	12,000	44	Eosinophiles = $0$ .
23	M.		12,500		Eosinophiles = 0.
58	M.		12,400		
58			12,400	60	
50	F.		12,300	00	
19	F.	3,104,000	12,300	35	Chronic diffuse.
59	M.	5,104,000	12,100	00	Chronic diffuse.
9	141.		11,900		Interstitial. Asthma.
63			11,400		ALLOCADOLOGIC ALCOCITATION

Table LIII., A.—Counts in Chronic Nephritis with Uræmia (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
44 31 48 44 31 45 34 30	M. M. F. F. M.	2,448,000 2,500,000	11,300 11,200 9,800 8,400 7,500 6,600 4,600 4,200	35 100 30	

Table LIII., B.—Chronic Diffuse and Chronic Parenchymatous Nephritis. No Uræmia.

Age.	sex.	White cells.	Age.	Sex.	White cells.	Age.	Sex.	White cells.
26		24,700	17	M.	10,400	28	M.	7,600
55		23,200	50		10,300	25	M.	7,600
21		19,000	43	F.	10,300	17	M.	7,500
55		18,500	20		10,200	55	M.	7,400
51		18,000	28		10,100	34	M.	7,400
45	M.	16,300	52		10,000	50	F.	7,300
11		16,000	60		10,000	26		7,300
66		15,800	20	F.	10,000	28	M.	7,000
43	M.	14,500	52	F.	9,800	42		7,000
19		14,300	30		9,500	41	M.	6,800
56	F.	14,000	25		9,000	8	M.	6,800
66	M.	14,000	24	F.	9,000	8	M.	6,500
47		13,100	36		8,800	39	M.	6,500
27	М.	13,000	54		8,700	7	M.	6,400
11	М.	13,000	45		8,300 April 5th	20	F.	6,250
38		12,800 April 4th			13,000	41	M.	5,500
		13,900 April 6th			April 9th.	42		5,500
		28,650	30	M.	8,300	30	F.	5,200
		April 9th, died.	27	F.	8,300	27	M.	5,100
16	F.	12.700	58.		8,200	30	M.	5,000
48		11,200	16		8,100	58	M.	4,800
25	M.	11,200	56		8,100	30	M.	4,500
10	F.	11,000	33	M.	. 7,900	41	M.	3,000
47	F.	10,800	14	M.	7,750	25		1,400
56	М.	10,700	15	F.	7,700			

The same wide range is seen in Table LIII., A and B, in which I have divided the uræmic and the non-uræmic cases into separate tables. It will be seen from these that thirty-four out of forty uræmic cases showed leucocytosis, while thirty-nine out of sixty-nine non-uræmic cases showed no leucocytosis. It is difficult to suppose that this is mere coincidence.

#### CHRONIC INTERSTITIAL NEPHRITIS.

Hayem found the fibrin more increased in this form of nephritis than in any other, and the anæmia less pronounced.

Grawitz distinguishes two stages:

- I. As long as the heart is strong enough to overcome the increased resistance at the periphery and the disturbances of circulation are not marked, the blood is normal.
- II. When compensatory hypertrophy is no longer sufficient to do the work of forcing the blood through the system, the usual effects of failing compensation (see Heart Disease, page 320) appear (dilution and subsequent concentration of the blood).

The white cells are normal.

TABLE LIV.—CHRONIC DIFFUSE NEPHRITIS; NO URÆMIA.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
20		3,492,000	39,000	42	With bronchitis.
26		3,500,000		50	With acute articular rheumatism.
36		2,560,000	16,100	35	April 14th.
		<u> </u>	12,400	20	April 30th.
			8,900		May 1st.
37		3,144,000	16,000	40	
11		3,660,000	15,600	52	
33		3,568,000	14,600	45	
22		4,272,000	14,400	45	Sub-acute.
19		5,864,000	14,300	65	Amyloid liver and spleen. February
					12th.
	İ	6,092,000	13,700		From ear.
		5,740,000	13,700		From finger.
24		3,824,000	11,400	55	
		4,268,000	13,600		
16		3,724,000	11,300	45	
35		3,164,000	10,600	50	Tertiary syphilis.
42		4,228,000	10,100	65	Œdema.
19		3,776,000	10,000	56	Cardiac hypertrophy.
28		4,560,000	10,000	45	
47		4,450,000	9,800	50	
21		4,080,000	8,600	70	
42		3,416,000	7,000	55	
55		4,360,000	6,300	50	Ascites.
24		4,800,000	5,700	65	
26	• •	1,468,000	3,800	23	Polynuclear, 70%; lymphocytes, 23%; large lymphocytes, 4.4%; eosinophiles, 2.6%; reds, megaloblasts, 3; normoblasts, 2; microblasts, 1. Considerable variation in size; many oval forms; considerable poikilocytosis.

Table LIV.—Chronic Diffuse Nephritis; No Uræmia (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
		1,136,000		19	Polynuclears, 71.8%; lymphocytes, 24.2%; large lymphocytes, 2.2%; eosinophiles, 1.2%; myelocytes, 6; megaloblasts, 6; normoblasts, 3. November 5th.
		1,752,000		22	Polynuclears, 69.4%; lymphocytes, 25.2%; large lymphocytes, 3.8%; eosinophiles, 1.6%; megaloblasts, 4; normoblasts, 2. November 13th.
		2,248,000		30	Polynuclears, 65.4%; lymphocytes, 28%; large lymphocytes, 3%; eosinophiles, 3.4%; basophiles, 2; megaloblasts, 1; normoblasts, 0. November 20th.
		2,540,000	••••	48	Polynuclears, 70.2%; lymphocytes, 23%; large lymphocytes, 2.6%; eosinophiles, 3.4%; basophiles, .8%. Red variation in size and shape less marked. Megaloblasts, 1. November 27th.
		3,392,000 3,580,000	5,800	60 65	December 6th.  Polynuclears, 79%; lymphocytes, 17.6%; large lymphocytes, 1.8%; eosinophiles, 1.6%. Reds stain well; slight poikilocytosis and variation in size; no nucleated reds.
36		5,060,000		75	Hemorrhagic nephritis.

TABLE LIV., A.—CHRONIC INTERSTITIAL NEPHRITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	29			23,700	65	
1 2 3	39	M.	6,040,381	19,000	80	Uræmic coma; moribund.
3		F.	[4,548,000]	15,000	50	Uræmic; mitral stenosis.
4	63		3,872,000	14,000	55	General paresis.
5	Adult	Μ.	4,244,000	12,000	67	Three and one-half hours after a meal.
6	22		5,020,000	11,200	50	,
6 7 8 9	46	M.		9,724		Uræmic; moribund.
8	47			7,300		
9	20	M.	4,088,000	6,000	66	March 23d.
				,	52	March 30th.
10	34	F.	3,536,000	8,300	57	
11	69	M.		8,500	87	
12	32	M.		6,000	65	
13	60			5,900		With mitral disease.

#### PYELO-NEPHRITIS.

Table LIV., B, speaks for itself. The anæmia is often severe and leucocytosis is the rule.

=						
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	24	F.	3,056,000	21,200	41	March 10th. Uræmia.
			2,976,000	15,200	38	March 13th.
			2,696,000	18,800	33	March 27th.
			3,272,000	25,200	33	April 14th.
2	26	F.	4,200,000	16,800		Perinephritic abscess too.
3	33	M.	4,536,000	15,550	36	Cystitis also.
4 5	26	F.	2,356,000	7,280	65	Cystitis also.
5	40			6,800	• • •	Pyelitis.

TABLE LIV., B.—PYELO-NEPHRITIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	55	М.	3,664,000	6,400		Adult cells, 72 per cent. Supposed cancer. Enormous firm tumor on each side. Autopsy.

The cases recorded in Table LIV., A, are probably not inconsistent with these rules. Of the seven cases with leucocytosis three were uræmic, and in a fourth the influence of digestion is seen. The hæmoglobin is lower than we should expect from Grawitz's account.

Uræmia, it would appear from these tables, may cause leucocytosis, or at any rate is not infrequently associated with it. Aside from uræmia and hemorrhage, nephritis probably does not cause leucocytosis.

#### STONE IN THE KIDNEY.

(See Table LV., A.) The state of the blood depends on the amount of ulceration caused by the stone; when this is considerable we have leucocytosis.

TABLE LV., A.-STONE IN THE KIDNEY.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1				22,800	85	Tender in loin.
2	51	• •		16,200 $16,500$ $10,800$		August 10th. August 12th. Pain gone.
3	19	M.		15,200		Much pus in urine.
$\frac{4}{5}$		M.	4,350,000		78	•
5	53			12,900	73	
6	20			10,200		
$\frac{7}{8}$	25	F.	4,160,000		65	
8	48	M.		8,990		
9	58	Μ.	5,680,000	8,000		
10			4,340,000	3,000		Much pus in urine.
			6,100,000	16,500		Two weeks later.
11	52	M.	3,048,000	7,500	30	
12	45	M.		7,500	95	
13	51	M.		6,000	95	Uric-acid stone passed.
14	30	M.		4,980	85	•
. !						

## Diagnostic Value.

Cancer would also cause leucocytosis, but would not increase fibrin as a rule, while most cases of stone with ulceration do increase fibrin.

#### FLOATING KIDNEY.

The blood is normal. This fact has some diagnostic value; for example, when we confound appendicitis with floating kidney, as has been done (see page 247). The presence of leucocytosis excludes the latter and favors the former. Most tumors or abscesses with which a floating kidney might be confused could be distinguished by the same criterion.

TABLE LV., B.—FLOATING KIDNEY.

No.	ge.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1 4	:7	• •	4,650,000	23,000 17,400 21,300 21,800	45	March 28th. Peritoneal inflammation.  April 4th. April 9th. April 15th. Diff. count 300. Polynuclear, 87 per cent; small lymphocytes, 7; large lymphocytes, 5.5; eosinophiles, .5; reds average size; very few poikilocytes.

TABLE LV., B.—FLOATING KIDNEY (Continued).

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
2 3	65		4,432,000	11,800	65	Double.
3	24			11,200	70	
4	37	F.	5,056,000	9,200	75	
4 5	41	F.	4,684,000	9,000	75	
6	24	F.		8,100		
7 8 9	67	F.		8,000	65	
8	23	F.	5,400,000	6,000	69	
	43	F.	4,700,000	2,400	76	
10	38	F.			75	Aneurism of arch also.
11	24	F.			80	
12	38	F.	4,416,000	5,800	67	
13	24	F.		7,600	80	

A large number of similar counts might be quoted.

#### HYDRONEPHROSIS.

TABLE LVI., C.—HYDRONEPHROSIS.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
52		4,016,000	16,400	75	March 7th.
4		5,496,000	$10,800 \\ 14,300$	60	March 12th.
	• •	0,400,000	28,600		Operation. Congenital.

#### PYO-NEPHROSIS.

Case I.—Female, 36; leucocytes, 16,200, of which 85 per cent are neutrophiles. Half a pint of pus found at operation.

Case II.—July 25th—Red cells, 3,856,000; white cells 9,800; hæmoglobin, 45 per cent. July 9th—Red cells, 3,450,000; white cells, 9,000; hæmoglobin, 55 per cent. August 3d—White cells, 6,650. August 6th—Operation. Pint of foul pus. Death.

#### DISEASES OF THE LUNGS.

#### BRONCHITIS.

"Acute catarrhal and chronic purulent bronchitis have relatively little leucocytosis in most cases" (v. Limbeck).

Except for this and a few other passing references, there is hardly anything in literature on the blood in bronchitis, so that I shall be forced to base my statements chiefly on the few counts recorded at the Massachusetts General Hospital.

#### ACUTE BRONCHITIS.

Aside from "capillary bronchitis," cases are not infrequently seen in which the signs are simply those of general bronchitis of the finer tubes, yet the symptoms are much more like pneumonia. Whatever may be the real conditions in the lungs of such patients, their blood is not infrequently exactly like that of pneumonia and does not help at all in the differential diagnosis between the two disease (see Cases 1 and 2, Table LVI., A).

TABLE LVI., A.—ACUTE BRONCHITIS.

Remarks   Red cells   White cells   Per cent hamoglobin   Remarks   Remark						
Remarks   Rema						
	Age.	Sex.	Red cells.	White cells.	hæmo-	Remarks.
	75		5 808 000	45 000	58	
To   F.   4,420,000   41,000   70   70   70   70   70   70   70	.0		0,000,000			Fourth day
70 F. 4,420,000					1	Eleventh day: died
56         F.         4,800,000         26,000         65         Temperature, 103°.           6          26,000          Whooping cough.           7         17,100          Fourth day; well.           32          23,500         80         With enteritis; temperature, 99°.           34          23,450         67         Temperature, 101°.           22         M.         23,450         67         Temperature, 101°.           21          22,200          Temperature, 101°.           7          21,200          Temperature, 101°.           8          19,000          Temperature, 103°.           31          19,000          Temperature, 100°.           36          19,000          Temperature, 99.5°.           36          17,200         62         Subacute.           41         F.         4,192,000         15,000          Four days later, temperature, 98°.           38          15,000          November 5th.	70	F	4 420 000			Die ventin day, died.
Section						Temperature 103°
28			,			
17,100		ì				
32	~					
34          23,500         80         With enteritis; temperature, 103°.           22         M.         23,450         67         Temperature, 101°.           21          22,200          Temperature, 101°.           7          20,400          Temperature, 103°.           44          5,660,000         20,100         58         Temperature, 100°.           31          19,000          Temperature, 100°.         Temperature, 99.5°.           36          19,000          Temperature, 98°.           50          17,200         62         Subacute.           42          17,000          Four days later, temperature, 100°.           41         F.         4,192,000         15,000         65         November 5th.           38          11,300          Temperature, 101.5°.           41         F.         4,192,000         15,000         65         November 25th.           55          18,800         60         Temperature, 101.5°.           22          13,000	32					
22 M. 23,450 22,200 21						
21 22,200 21,200 21,200 20,400 44 5,660,000 20,100 31 19,100 Temperature, 100°. Temperature, 99.5°. 36 19,000 58 17,200 62 Subacute. 17,000 15,000 15,000 11,300 11,300 16,400 55 13,000 16,300 16,400 55 13,000 16,300 16,400 55 13,000 16,300 16,400 55 13,000 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300 11,300						
7						
58          20,400           44          5,660,000         20,100         58         Temperature, 108°; asthma.           31          19,100          Temperature, 100°.           36          19,000          Temperature, 99.5°.           50          17,200         62         Subacute.           42          15,000          First day; temperature, 100°.           41         F.         4,192,000         15,000         65         November 16th.           11,300          November 25th.         November 25th.           15,000          Subacute; temperature, 100°.           26         M.         14,200         70         Temperature, 101.5°.           22          13,800         60         Temperature, 102°.           38          13,000          Temperature, 100°.           55          13,000          Temperature, 100°.           55          13,000          Temperature, 100°.           55          13,000          Temperat						
34          5,660,000         20,100         58         Temperature, 100°, asthma.           31          19,000          Temperature, 100°, asthma.           36          19,000          Temperature, 99.5°, asthma.           36          19,000          Temperature, 98°.           50          17,200         62         Subacute.           42          17,000          First day; temperature, 100°.           41         F.         4,192,000         15,000          Temperature, 103°.           41         F.         4,192,000         65         November 5th.         November 16th.           11,300          Subacute; temperature, 100°.         Temperature, 101.5°.           22          13,800         60         Temperature, 102°.           23          13,000          Temperature, 100°.           55          13,000          Temperature, 100°.           55          13,000          Temperature, 100°.           5          13,000						Tomporarato, 100 (
31          19,100          Temperature, 100°.           3          19,000          Temperature, 99.5°.           36           17,200         62         Subacute.           42          17,000          First day; temperature, 100°.           41         F. 4,192,000         15,000          Four days later, temperature, 103°.           41         F. 4,192,000         15,000          November 5th.           11,300          November 25th.            55          13,800         60         Temperature, 101.5°.           22          13,800         60         Temperature, 102°.           55          13,000          Temperature, 102°.           55          13,000          Temperature, 102°.           55          13,000          Temperature, 100°.           5          13,000          Temperature, 100°.           5          13,000          Temperature, 100°.           5        <		1			58	Temperature, 103°: asthma.
3          19,000          Temperature, 99.5°.           50          17,200         62         Subacute.           42          17,000          First day; temperature, 100°.           41         F. 4,192,000         15,000          Temperature, 103°.           41         F. 4,192,000         15,000          November 5th.           11,300         17,600          November 16th.           17,600          November 25th.           26         M.         14,200         70           22          13,800         60           16,300          Temperature, 101.5°.           22          13,000            55          13,000            16,400          Sixth day.           55          13,000            13,000          Temperature, 100°.           5          13,000            11,300          Sixth day; temperature, 101°.           23          12,600						
36          19,000          Temperature, 98°.           50          17,200         62         Subacute.           42          15,000          First day; temperature, 100°.           38          15,100          Temperature, 103°.           41         F.         4,192,000         15,000         65         November 5th.           41         F.         4,192,000         65         November 16th.           17,600          November 25th.           November 25th.         Subacute; temperature, 100°.           26         M.         14,200         70         Temperature, 101.5°.           22          13,800         60         Temperature, 102°.           23          13,000          Temperature, 100°.           5          13,000          Temperature, 100°.           13,300          Temperature, 102.5°.           11,300          Sixth day; temperature, 100°.           23          12,600          Temperature, 101.5°           30          12,600 <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>						
50 17,200						
17,000		1				
15,000		Į .				First day; temperature, 100°.
Third day.   Temperature, 100°.   Temperature, 101°   Temperature, 101°.   Temperature, 101°.   Temperature, 101.5°.   Temperature, 101.5°.   Temperature, 101.5°.   Temperature, 101.5°.   Temperature, 101°.   Temperature, 101.5°.   Temperature, 101.5°.   Temperature, 102°.   Temperature, 102°.				15,000		Four days later, temperature, 98°.
11,800	38			15,100		Temperature, 103°.
11,300	41	F.	4,192,000	15,000	65	November 5th.
55				11,300		November 16th.
26 M				17,600		November 25th.
22	55			15,000		Subacute; temperature, 100°.
16,300		M.				
55	22				60	Temperature, 102°.
55						
5 13,000 Temperature, 102.5°. Third day; temperature, 101° Sixth day; temperature, 100°. Sixth day; temperature, 100°. Eleventh day; temperature, 98°. 12,600 Temperature, 101.5° Temperature, 101.5° Temperature, 102°.						
12,600 Third day; temperature, 101° Sixth day; temperature, 100°. Sixth day; temperature, 100°. Eleventh day; temperature, 98°. Temperature, 101.5° Temperature, 101.5° Temperature, 102°.	55					
11,300 Sixth day; temperature, 100°. Eleventh day; temperature, 98°. Temperature, 101.5° Temperature, 102°.	5					
23						Third day; temperature, 101°
23 12,600 Temperature, 101.5° 30 12,000 65 Temperature, 102°.						Sixth day; temperature, 100°.
30 12,000 65 Temperature, 102°.						Eleventh day; temperature, 98°.
00   17   6 106 000   10 000					65	Temperature, 102°.
28   F.   6,196,000   12,000	28	F.	6,196,000	12,000		

TABLE LVI., A.—Acute Bronchitis (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
46	M.		11.800		Temperature, 104°.
13			10,800		Temperature, 102°.
20	M.		10,600	65	Temperature, 104°.
40	M.		10,300		Temperature, 101°.
31			10,200		Temperature, 102°.
69			9,400		Temperature, 101°.
42	M.		9,300		
50	F.	5,260,000	8,000	72	
50	M.	5,952,000	7,900	50	
38			7,800		Temperature, 99°.
48			7,800		Temperature, 102°.
25			7,200		Temperature, 100°.
52	M.		7,000	70	
25	M.		7,000	74	Temperature, 103°.
56	F.		6,800		
36	М.	4,392,000	6,000	72	October 31st.
			8,600		November 3d.
43			5,900	::	Temperature, 100°.
29	Μ.		4,000	80	Temperature, 102°.

TABLE LVI., B.—CHRONIC BRONCHITIS.

					Per cent		
No.	Age.	Sex.	Red cells.	White cells.	hæmo- globin.	Remarks.	
1	51			38,000			
1 2 3	24			29,500			
3	Adult	M.	3,680,000	18,500	63		
4 5	68			16,400		With emphysema.	
5	48	M.		15,000		Chronic febrile, with laryngitis.	
						Recovery.	
6	64			15,000		Temperature, 98.6°.	
6 7 8 9	62			14,300		Temperature, 100°; with asthma.	
8	65			12,900		Fibrinous.	
	60			10,500			
10	43			11,000		Temperature, 98°; chronic with emphysema.	
11	74			8,900		Temperature, 98°.	
12	27	F.	5,384,000	8,800	73	Constipation; neurasthenia; two weeks afebrile.	
13	61	M.	4,300,000	8,000	63	Five months.	
14	20	F.		7,925	78		
15	18	М.		7,792		Keratitis, conjunctivitis. No symptoms.	
16	26	F.	4,700,000	6,700	70	Asthma.	
17	29	F.	4,100,000	5,500	61	Empyema of the antrum.	
18	20	М.		5,062		One month.	

In the majority of acute cases, however, the blood shows no changes unless concentration due to cyanosis be present.

In chronic cases (Table LVI., B) leucocytosis is very uncommon; more so, I think, than the table represents. If more counts were added, nearly all, I think, would be normal.

The red cells and hæmoglobin show no changes to speak of in either acute or chronic cases.

The blood has no diagnostic value so far as I know except that when pneumonia is in question a normal count of white cells speaks against it and in favor of bronchitis. If emphysema is also present, it sometimes produces a condition of the blood different from that in simple bronchitis.

#### EMPHYSEMA AND ASTHMA.

Grawitz reports an increase in the number of red cells in emphysema, which he believes to be due to cyanosis, and this covers up the really anæmic condition of the blood of many patients. Practically the same conditions are present as in the cyanosis of heart disease (see page 320) and the concentration of the blood is brought about in the same way. Leichtenstern' noticed a diminution in hæmoglobin at the time when the heart first fails, due probably to the diminished blood pressure which allows the lymph from neighboring tissues to flow into the vessels and dilute the blood.

In both asthma and emphysema it has been noted by Müller,<sup>2</sup> Gollasch,<sup>3</sup> Gabritschewsky<sup>4</sup> and others that *eosinophiles* are very numerous in the sputum, and Fink<sup>2</sup> also noted an increase of the same cells in the blood, running as high as 14.6 per cent instead of the normal one to two per cent. This increase is present only at the time of the paroxysm and for a short time before and after it. Von Noorden found in one case 25 per cent of eosinophiles during an attack, and a few days later could discover but one eosinophile in twelve cover slips. In another case, after five attacks on successive days, the eosinophiles were 33 per cent. Billings<sup>5</sup> reports the following counts:

<sup>&</sup>lt;sup>1</sup> "Ueber das Hb-Gehalt des Blutes," etc., Leipzig, 1878.

<sup>&</sup>lt;sup>2</sup> Ref. in Fink, "Beiträge z. Kennt. des Eiters," Dissert., Bonn, 1890.

<sup>&</sup>lt;sup>3</sup> Fortschritte der Med., 1889.

<sup>&</sup>lt;sup>4</sup> Arch. f. exp. Path. und Pharm., 1890, p. 83.

<sup>&</sup>lt;sup>5</sup> New York Med. Journal, May 22d, 1897.

	January 26th.	February 4th.	February 11th.
Red cells.		4,221,000	4,630,000
White cells		7,500	7,600
Hæmoglobin	68 per cent.	75 per cent.	86 per cent.
Polymorphonuclear	_		_
cells	36 "		
Lymphocytes (small)	5 "		
Lymphocytes (large)	5.2 "		
Eosinophiles	53.6! "	38.2 per cent.	33.9 per cent.
	Few normoblasts		No nucleated red cells.

Their presence in increased numbers before a paroxysm is said to make it possible to predict its coming (v. Noorden, Schwerskewski). Coler reports a case of asthma with a leucocytosis of 52,000, 25 per cent of which was made up of eosinophiles. The case was complicated with extensive purpura, painful muscles, and extreme cyanosis, but microscopic examination of the affected muscles showed no trichinæ.

I have watched one subacute case without well-marked paroxysms or periods of perfect health. The blood was frequently examined and showed always a slight leucocytosis with 11 to 15 per cent of eosinophiles. As this applies only to pure bronchial asthma and not to cases secondary to disease of the heart or kidney, Schreiber states that we are enabled to distinguish bronchial from cardiac or renal asthma by the increase of eosinophiles in the blood and sputa in bronchial cases, which does not occur in asthma due to cardiac and renal trouble. Other records are (Gabritschewsky):

Case I.—White cells .	 . 8,200
Eosinophiles.	 10.8 per cent.
Case II.—White cells	 . 6,800
Eosinophiles.	 22.4 per cent.
Polynuclears.	 35 "

#### ASTHMA.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
26	M.		32,500		Fifth. Temperature 100°. Bronchitis and emphysema.
			19,200		Seventh. Temperature normal.
50	F.		19,800	50	Typical bronchial asthma during
70	M.	5,500,000	13,000	• -	paroxysm. Chronic asthma and emphysema in paroxysm; polynuclear cells, 79 per cent.
29	M.		9,750		

For Pheumonia, see page 189. For Phthisis, see page 271. For Abscess of Lung, see page 252.

#### SYPHILIS OF THE LUNG.

In a case of syphilitic infiltration of the lung (autopsy—Drs. Councilman and Wright) recently observed at the Massachusetts General Hospital the leucocytes rose rapidly from 8,700 to 27,400 as death approached.

#### GANGRENE OF LUNG AND ABSCESS.

Age.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
49		39,900		Abscess, autopsy.
42		22,400		Abscess after grippe.
19		18,400		Gangrene.
48		16,400		Abscess after immersion.
54		15,300		First day. Gangrene.
		20,500		Fourteenth day.
		18,300		Sixteenth day.
		23,000		Nineteenth day.
		27,000		Twenty-first day.
		27,000		Twenty-sixth day.
		31,000		Twenty-ninth day.
		17,000		Thirty-second day. Better.
		20,000		Thirty-sixth day.
		15,800		Fifty-fourth day.
50		9,600		Gangrene.

# PART V.

# DISEASES OF THE NERVOUS SYSTEM, CONSTITUTIONAL DISEASES, AND HEMOR-RHAGIC DISEASES

# CHAPTER VIII.

#### DISEASES OF THE NERVOUS SYSTEM.

#### NEURITIS.

In cases of multiple neuritis, febrile and apparently of an infectious nature, the following counts are found in the records of the Massachusetts General Hospital:

Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
• •		4,816,000	25,000 24,800 18,700	42	July 10th. Temperature, 101°. July 13th. July 16th.
		4,320,000	$\begin{array}{c} 21,000 \\ 16,000 \\ 28,700 \\ 19,500 \end{array}$	60	July 20th. July 25th. July 31st. No fever. August 7th. No fever.
24			23,200 8,400		August 20th. No fever. Polynuclear, 36%. Lymphocytes, 62%. Eosinophiles, 2.
22			6,400		(Count, 300 cells.)

The first case, a boy of eleven, recovered and left the hospital well.

But these changes occur also in alcoholic (afebrile) neuritis, as the following counts show:

Age.	Sex.	Red cells.	White cells.	Per cent hæmoglobin.		Remarks.
0			16,100		Pneumonia.	No autopsy.
		3,608,000	15,000	75		
		3,260,000	14,000	64		
			13,700	60		
39		3,584,000	12,000	45		
			11,200	68		
			7,700	80		
25			7,600			
			6,700	82		

In all cases the counts were made just at meal time, so that the leucocytosis is not due to digestion. Gastritis was not present in either case.

One case of post-diphtheritic neuritis in a child of eight showed the presence of anæmia only: Red cells, 3,850,000; white cells, 7,393; hæmoglobin, 70 per cent.

Neuritis in lead poisoning does not affect the count of leucocytes, as twenty-five eases studied at the Massachusetts General Hospital have shown.

HERPES ZOSTER.

No.	Age.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
1	52		15,500		Temperature 99°.
2	74		9,100	::	•
3	53		8,500	60	

Neuralgia, whether facial, intercostal, sciatic, or ovarian, showed normal blood in numerous cases examined at the Massachusetts General Hospital.

#### DISEASES OF THE BRAIN.

Meningitis (see Inflammation of Serous Membranes, page 266). Zappert in one case of brain abscess found only 4,000 white cells.

In pachymeningitis hæmorrhagica and cerebral syphilis (one case of each) v. Jaksch found leucocytosis. My own experience has been the same.

Cerebral and cerebellar tumors have no effect on the blood as far as could be judged from nine counts in the former and three in the latter disease. Von Jaksch found slight leucocytosis in two cases of brain tumor and one of cysticercosis. Zappert found normal blood in one case of cerebral tumor.

TABLE LVII.—CEREBRAL TUMOR.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
43			18,100	70	
38			16,900	75	
43 38 22			15,000		
13			14,500		
			13,700		
26			12,500		
4			12,200	70	· · · · · · · · · · · · · · · · · · ·
27			10,600	60	
33			9,000	72	
4 27 33 52			7,000		
31			4,100		

 $Fresh\ cerebral\ hemorrhage$  usually causes leucocytosis, as the following table shows:

TABLE LVIII.—CEREBRAL HEMORRHAGE.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
42	M.		31,000	95	Autopsy.
52	M.		30,000	00	Polynuclear cells, 92%.
0.0	111.	5,512,000	25,000	85	Autopsy.
60		0,012,000	29.700		Autopsy.
60			23,600		Tratopsy.
00			26,000		Second day.
55			22,200		Coma.
69			19,800		Coniu.
47	M.		19,400		Autopsy.
54	11.2.		19,000	65	Tratopsy.
56			17,400	100	Coma. Hemiplegia.
70	F.		16.800	68	Hemorrhage four days before count.
• •			20,000		Autopsy.
		5,560,000	15,600	90	zzacopoj.
59			16,000		
62			14,900		Temperature, 104.7°. Died.
52			13,800		Hemiplegia. Died.
48			13,000		Hemiplegia. Coma.
37	M.		12,300	70	1-10-11
68			12,000		
			11,900		No coma.
55			11,800		
42			11,600		
38	M.		10,400	58	Conscious; recovered.
37	M.		10,300	90	Autopsy.
65	M.		10,200	60	
60			10,200	70	
65		952,000	5,200	18	Arterio-sclerosis; emphysema of
					lungs; pernicious anæmia. Tem-
					perature, 102°.
					Polynuclear, 84.2%.
					Lymphocytes, 13.8%.
					Eosinophiles, .8%.
					Myelocytes, .8%.
					Basophiles, .2%.
					Megaloblasts = 6.

#### CAISSON DISEASE.

Age.	White cells.
	. 18,900
30	. 10,700

#### CHOREA AND TETANY.

Chorea showed in twelve cases normal blood except for increased percentages of eosinophiles, as in Zappert's four cases, counted 630–1,360 (8–19 per cent of eosins).

Burr has made a careful study of the blood in thirty-six cases and arrived at the following conclusions: There is usually a slight diminution in red cells and a moderate diminution in hæmoglobin. Any severe grade of anæmia is due to some complication. He did not record the leucocytes. Tetany shows no blood changes.

#### DISEASES OF THE SPINAL CORD.

Chronic diseases of the spinal cord, such as tabes dorsalis, syringomyelia, spastic paraplegia, diffuse myelitis, paralysis agitans, and progressive muscular atrophy, are found to produce no changes in the blood.

For Spinal Meningitis, see page 267.

#### GENERAL PARALYSIS OF THE INSANE.

Capps' has made a careful study of the blood in nineteen cases and comes to the following conclusions:

- 1. Red corpuscles and hæmoglobin are always slightly diminished, the averages being 4,789,900 and 85 per cent.
- 2. Most cases show a slight leucocytosis—22 per cent above the normal on the average. Early cases may have no leucocytosis.
- 3. The differential counts show that the blood is slightly older than that of normal adults. The polymorphonuclear leucocytes average nearly 74 per cent and the smaller forms of lymphocytes only 14.2 per cent, while the larger forms of lymphocytes are relatively numerous, averaging 7.8 per cent. In a few cases the eosinophiles were very numerous<sup>2</sup> (8.7 and 6.4 per cent).
  - 4. At the time of convulsions the red cells and hæmoglobin are
    - <sup>1</sup> American Journal of the Medical Sciences, July, 1896.
- <sup>2</sup> Roncoroni (Archiv di Psichiat. Scien., 1894, p. 293) finds eosinophiles increased even to twenty-five per cent in the agitated and violent cases.

apparently increased (due no doubt to the violent muscular contractions which raise blood pressure and concentrate the blood, or to cyanosis).

There is a sudden and pronounced increase in the leucocytes during and after convulsions or apoplectiform attacks. That this is not due to concentration of the blood or to stasis, Capps thinks is shown by the fact that not only the number, but the differential count of white cells shows changes, the "large mononuclear" cells being relatively increased, sometimes as high as 25 per cent. Myelocytes were seen in one case after the convulsions, and especially just before death, when in a leucocytosis of 18,250 11 per cent were myelocytes.

#### HYSTERIA AND NEURASTHENIA: HYPOCHONDRIASIS.

A large number of cases have been counted at the Massachusetts General Hospital, with a view of excluding other diseases. The blood count is always normal except that in a certain number of the hysterical cases eosinophiles are relatively increased, and that many of the neurasthenics show the increased percentage of lymphocytes which I have alluded to above (page 114) as characteristic of a variety of debilitated conditions.

Marked anæmia is seldom present, although the hæmoglobin is not infrequently as low as 65 per cent. Reinert<sup>2</sup> found the hæmoglobin under 60 per cent in only 4 out of 48 cases of hysteria, and in none of 36 neurasthenics.

The value of the blood examination in such cases, like that of the urine or the lungs in hysteria, is as negative evidence, and in this respect it is important. When the discrepancy between com-

¹Leucocytosis has been repeatedly noticed in convulsions from various causes. Probably the irritant which causes the motor discharge also acts on the leucocytes by chemotaxis. For example Barrows' study of 8 cases of insanity with convulsions includes counts of—1, 43,000 leucocytes with 92 per cent of polynuclears; 2, 33,000 leucocytes with 83 per cent of polynuclears; 3, 32,400 leucocytes with 85 per cent of polynuclears and 9 per cent of myelocytes; 4, 21,500 leucocytes with 88 per cent of polynuclears. These counts were made immediately after a series of convulsions. The leucocytosis lasted for many hours and showed the characteristics of ordinary infectious leucocytosis.

In convulsions from improper feeding in infancy I have seen the leucocytes rise from 13,500 before the fit to 27,800 after it.

<sup>&</sup>lt;sup>2</sup> Münch, med. Woch., 1805, No. 14.

plaints and signs is great, we want to be doubly sure that nothing hidden escapes our notice, and the blood examination is one of the most valuable adjuvants we have in the discovery of deep-seated inflammation or malignant disease, as well as in giving us a general measure of the patient's degree of bodily health as distinguished from nervous force. The former may be high when the latter is low, or both may be low, and the distinction marks out two classes of cases in which somewhat different treatment is appropriate. There is no use in undertaking to make "blood and fat" when the patient has already plenty of each, though it may be well to carry out the same régime as a matter of suggestion.

#### MENTAL DISEASES.

The association of anemia with insanity is too frequent to be a mere coincidence, though it is hard to make either serve as a cause for the other. Very possibly they should both be looked upon as symptoms of a common underlying (unknown) cause.

This form of anæmia has been noticed by Houston¹ in melancholia and general paralysis, and by Smith² in various forms of insanity.

Krypiakiewicz<sup>3</sup> noticed an increase of eosinophiles in acute forms of insanity, but not in the chronic forms. The *leucocytosis of acute delirium*<sup>4</sup> is exemplified by the following case from the Massachusetts General Hospital records:

A girl of fifteen; acute delirium; leucocytes, 12,750; no food for eight hours; red cells, 4,510,000; hæmoglobin, 63 per cent.

Puerperal mania is to be distinguished from the delirium of puerperal sepsis by the fact that the latter shows leucocytosis with increased percentage of polymorphonuclear cells, while the former has no leucocytosis (if uncomplicated) and the eosinophiles are apt to be increased of (diminished in sepsis).

A case of puerperal mania seen by the writer showed: Red cells, 5,210,000; white cells, 6,500; hæmoglobin, 84 per cent; eosinophiles, 8 per cent.

<sup>&</sup>lt;sup>1</sup> Houston: Boston Med. and Surg. Journal, January 11th, 1894.

<sup>&</sup>lt;sup>2</sup> Smith: Jour. of Ment. Sci., October, 1890.

<sup>&</sup>lt;sup>2</sup> Krypiakiewicz: Wien. med. Woch., 1892, No. 25.

<sup>&</sup>lt;sup>4</sup>Ref. in Klein-Volkmann's "Sammlung klin. Vorträge," December, 1893.

<sup>&</sup>lt;sup>5</sup> Neusser: Loc. cit.

#### CONSTITUTIONAL DISEASES.

#### OBESITY.

Oertel distinguishes a plethoric and an anæmic form of obesity not merely elinically, but by the evidence of post-mortem examinations. He believes that there is a real over-filling of the vessels in the first. The second form occurs most often in women.

Kisch examined (with v. Fleischl's instrument) the hæmoglobin of 100 obese patients; 79 showed over 100 per cent of hæmoglobin, 1 reaching 120 per cent, while the other 21 were anæmic.

#### DIABETES.

There is nothing characteristic about the blood except the increased amount of sugar to be detected (.57 per cent as against .1 per cent normally); but this is not a clinically applicable test.

Two simple tests for diabetic blood have recently attracted attention:

- 1. Bremer's test: Heat thick-spread blood films to  $135^{\circ}$  C.; cool and stain with one-per-cent aqueous solution of Congo red for two minutes. The blood if diabetic looks yellow (to the naked eye). Normal blood similarly treated looks red. Staining with methyl blue also shows a difference between normal blood and diabetic blood. The normal is blue, the diabetic yellowish green.
  - 2. Williamson's test: Make a mixture of

Blood	20 c.mm. (2 drops).
Aqueous methyl blue (1:6,000)	1 c.c.
Liquor potassæ, 60 per cent (sp. gr., 1.058)	40 c.c.
Water	40 c.c.

Let the mixture stand three to four minutes in boiling water. With diabetic blood the mixture turns yellow, with normal blood it does not. Williamson has found this test positive in eleven diabetics and negative in one hundred cases of other diseases. Bremer claims that by his method cases of diabetes can be recognized before sugar appears in the urine or after it has (temporarily) disappeared. Le Goff confirms the value of the test. Eichner and Folkel find Bremer's reaction to be as stated, but find similar color changes in leukæmia, Hodgkin's disease, and Graves' disease, and changes

something like it in a variety of cachectic conditions. Badger has studied the blood of diabetics, leukæmics, cases of Graves' disease, and other cases at the Massachusetts General Hospital. Only in Graves' disease did he find reactions like those of diabetic blood.

The alkalinity has been said to be greatly diminished, especially in the fatal coma, but v. Noorden thinks the tests are unreliable.

Fat is often increased in the blood, up to about twelve times the normal, so that the serum is milky, and glycogen has been demonstrated microchemically in the corpuscles.

#### Red Cells.

Sugar in the blood draws water from the tissue into the vessels, thereby diluting the blood; but in a short time the blood frees itself of the excess of sugar and fluid through increased diuresis so as to concentrate the blood.

These two alternating influences serve to explain the widely different counts of different observers.

Toward the end of the disease a decided *cachexia* often develops, the anæmia of which may be temporarily covered up by the concentration above noted, or accentuated by the *dilution* which sometimes occurs. Accordingly we may find the corpuscles increased, normal, or diminished in different cases or at different times with the same case.

Grawitz counted 4,900,000 red cells in a patient in comparatively good health, and three weeks later, when the patient had just been seized with the fatal coma, the count showed 6,400,000 per cubic millimetre.

The white cells show no constant changes, except that v. Limbeck has noted in several cases that the digestion-leucocytosis is unusually large even without previous fasting. Von Jaksch found leucocytosis in one of his eight cases, but on this point as on many others his results are almost unique. The only similar observation is that of Habershon, who reports moderate leucocytosis, decreased by strict diet. In thirteen cases I have never seen leucocytosis. One case of diabetic coma showed 4,200 leucocytes per cubic millimetre. Another in a child of eight years showed 49,000 white cells.

<sup>&</sup>lt;sup>1</sup>St. Bartholomew Hosp. Report, 1890, p. 153.

#### GOUT.

A few cubic centimetres of serum from gouty blood made acid with acetic acid (six drops of a twenty-eight-per-cent solution to every drachm of serum) deposit crystals of uric acid on a thread in from eighteen to forty-eight hours; but this is not always to be found, and is by no means peculiar to gout.¹ Uric acid is to be found in the blood in pneumonia, cirrhotic liver, nephritis, grave anæmia, leukæmia, and gravel; also in health and after a meal of calf's thymus or any food containing much nuclein.

The red corpuscles show no special changes except in severe chronic cases, which are sometimes anæmic. The white cells are increased according to Neusser, while v. Limbeck and Grawitz found the blood wholly normal.

It is particularly in this disease that Neusser supposed the "perinuclear basophilic granulations" to exist in the white cells, which condition he believes to be characteristic of any "uric-acid diathesis." Futcher has conclusively disproved this. Fibrin is increased in acute cases.

Ewing states that he found "uniform but moderate anæmia in a series of chronic cases examined at Roosevelt Hospital, the patients all coming from the poorer classes. In the chronic cases leucocytosis of moderate grade may be observed, but it is difficult to determine its relation to the gouty process, as many of these patients suffer from other complaints."

#### MYXŒDEMA.

Le Breton<sup>2</sup> examined the blood in one case both before and after thyroid treatment, and found that after forty days' treatment the red cells had risen from 1,750,000 to 2,450,000, the white cells from 4,500 to 9,600, and the hæmoglobin from 65 to 68 per cent.

The remarkably high color index in this case before treatment (nearly 2.!) corresponds with the observations of Le Breton in the dried specimen, which showed a decided increase in the size of the

 $<sup>^{\</sup>rm I}$  It is important to evaporate the serum at a temperature not above 70° F., otherwise crystals will not form.

<sup>&</sup>lt;sup>2</sup> Le Breton: Ref. in Wien. med. Blätter, 1895, p. 49.

red corpuscles. He also noticed before instituting the thyroid treatment the presence of nucleated red cells and an excess of the polymorphonuclear form of leucocytes. Under treatment the nucleated red cells disappeared and the lymphocytes rose to their normal per cent.

Putnam' has watched a similar case in which the number of red cells rose from 3,120,000 to 5,700,000 under thyroid treatment.

Murray<sup>2</sup> has collected 23 cases with blood examinations. Of these cases, 7 showed a normal blood count, 10 were anæmic, 4 showed leucocytosis, and 2 exhibited both anæmia and leucocytosis.

Kraepelin<sup>3</sup> noticed (like Le Breton) a marked increase in the average diameter of the corpuscles in three cases, even when the count and the hæmoglobin were normal.

I have had an opportunity to examine the blood in four cases of this disease, but did not find anything remarkable in any one of them.

Case.	Red cells.	White cells.	Per cent Hæmoglobin.	Remarks.
1	4,670,000	6,000	87	Count 400 cells: Polynuclear, 66%; lymphocytes, 31.5%; eosinophiles, 2.5%; slight deformity of reds; 1 normoblast.
2	4,460,000	8,800		
3	4,856,000	5,200	80	
4	4,012,000	7,900	45	

Differential counts were made in three cases, and no increase in the size of the corpuscles, such as Le Breton and Kraepelin saw, was present in these cases. The count showed:

Case.	Polymorphonuclear cells.	Lymphocytes.	Eosinophiles.
1	67	28 27.8 26	5 4.4

<sup>&</sup>lt;sup>1</sup> Putnam: Ref. in Murray's article in "Twentieth Century Practice of Medicine," vol. iv.

<sup>&</sup>lt;sup>2</sup> Murray: "Twentieth Century Practice of Medicine," vol. iv., p. 710.

<sup>&</sup>lt;sup>3</sup> Kraepelin: Deut. Arch. f. klin. Med., vol. xlix., p. 587.

The increase of eosinophiles in two of these cases may perhaps be due to the skin troubles in the disease.

J. J. Thomas found a few myelocytes in a case of Putnam's.

### CRETINISM.

Koplik¹ records the following in two cases of sporadic cretinism: Case I.—Fifteen months old; advanced stage of disease. Hæmoglobin, 18 per cent.

Case II.—Red cells, 3,026,000; white cells, 13,500; hæmoglobin, 105 per cent. This high hæmoglobin corresponds to *normal fætal* blood. The child was nine weeks old, but its backward development is mirrored in the blood. As the case improved under thyroids the hæmoglobin came down.

# GRAVES' DISEASE (BASEDOW'S DISEASE; EXOPHTHALMIC GOITRE).

The blood is normal, except for an occasional associated chlorosis and sometimes a marked lymphocytosis. In one case I found 51.3 per cent of lymphocytes and 1 per cent of myelocytes in 1,000 leucocytes, the polymorphonuclear cells being only 48 per cent; but in fourteen other cases I have never found this again. The same fact has been noticed by Neusser (cited in Klein, loc. cit.).

Oppenheimer<sup>2</sup> found the red cells and hæmoglobin normal in two cases. Von Jaksch<sup>3</sup> in one case "complicated with myxædema" found 3,818,000 red and 8,000 white cells.

The association of Graves' disease with chlorosis is illustrated by two cases from Zappert:<sup>4</sup>

Case.	Red cells.	White cells.	Per cent Hæmoglobin,
1	2,858,000	3,800	32
	2,738,000	3,800	30

The same writer found eosinophiles much increased (8.5 per cent) in one out of four cases.

<sup>&</sup>lt;sup>1</sup> New York Medical Record, October 2d, 1897.

<sup>&</sup>lt;sup>2</sup> Deut. med. Woch., 1889, p. 861.

<sup>&</sup>lt;sup>3</sup> Zeit. f. klin. Med., 1893, p. 187.

<sup>&</sup>lt;sup>4</sup> Zeit. f. klin. Med., 1893, p. 266.

	Age.	Sex.	Red cells.	White cells.	Per cent Hæmoglobin.	Remarks.
1 2 3 4 5	41 27 42 33 41	M	3,668,000 4,920,000 4,464,000 4,584,000	2,800 7,300 7,700 9,800 12,500 12,700 16,000 15,000	45 65 60 63 50 	Died. January 13. January 31. February 13. February 15.

MASSACHUSETTS GENERAL HOSPITAL CASES.

### ADDISON'S DISEASE.

Some, but not all, cases are accompanied by marked anæmia. Neumann¹ observed a case in which the symptoms came on acutely and the red cells sank to 1,120,000 per cubic millimetre. During the convalescence which followed, the cells ran up above normal, reaching 7,700,000.

Tschirkoff <sup>2</sup> reports two cases in which the red cells were respectively 3,280,000 and 2,933,000 at the lowest, but whose hæmoglobin was extraordinarily high, over 100 per cent in one case. This he found on spectroscopic examination to be due to a great increase of reduced hæmoglobin in the corpuscles. Methæmoglobin was also noted.

The white corpuscles showed no changes, quantitative or qualitative, except that they contained black pigment granules. Three cases have been examined at the Massachusetts General Hospital. The first, a woman of thirty, showed 6,240,000 red cells with 14,000 white, and 90 per cent of hæmoglobin. The differential count of 900 leucocytes showed the following figures: Polymorphonuclear cells, 53.4 per cent; lymphocytes, 41 per cent; eosinophiles, 4.5 per cent; myelocytes, .9 per cent.

The eosinophiles were very large, some of them eosinophilic myelocytes.

The second, a man of forty-two, was very anæmic and weak at entrance and showed: Red cells, 2,196,000; white cells, 7,500; hæmoglobin, 20 per cent. Differential count of 200 leucocytes showed: Polymorphonuclear cells, 65 per cent; lymphocytes, 31.5

<sup>&</sup>lt;sup>1</sup> Neumann: Deut. med. Woch., 1894, p. 105.

<sup>&</sup>lt;sup>2</sup> Zeit. f. klin. Med., 1891, vol. xix., Suppl. Heft 37.

per cent; eosinophiles, 3.5 per cent; 5 normoblasts; marked poikilocytosis.

Under suprarenal extract his blood improved in a month till his red cells numbered 4,700,000; white cells, 9,000; hæmoglobin, 65 per cent.

The third, a man of fifty-two, showed: October 20th—red cells, 2,848,000; white cells, 4,800; hæmoglobin, 45 per cent. December 10th—red cells, 2,624,000; white cells, 7,100; hæmoglobin, 45 per cent. Differential count: Polynuclear, 74 per cent; small lymphocytes, 22 per cent; large lymphocytes, 4 per cent; eosinophiles, .4 per cent. No nucleated red cells.

A fourth patient, kindly sent me by Dr. Rogers, of Dorchester, showed: Red cells, 2,864,000; white cells, 2,000; hæmoglobin, 51 per cent. Differential count of 300 cells showed: Polymorphonuclear cells, 63.3 per cent; lymphocytes, 33.3 per cent; eosinophiles, 2.3 per cent; basophiles, .3 per cent.

I have never seen melanin in the leucocytes as Tschirkoff did in his two cases.

Age.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
34 39 29	5,056,000 5,460,000 4,804,000	5,000 117,000 10,000	60 80 68	Soon died. Autopsy. Polynuclear, 77.6 %. Lymphocytes, 14.0 Eosinophiles, 8.0
	519,200	10,400	80	Myelocytes, .4

Addison's Disease.

### OSTEOMALACIA.

The blood has for a long time been supposed, on the authority of v. Jaksch (Zeit. f. klin. Med., vol. xiii., page 360), to exhibit a diminished alkalinity, the bones being supposed to be eaten away by acids in the blood. Von Limbeck and many other observers have lately shown that the blood is normal in alkalescence.

Corpuscles and hæmoglobin are usually within normal limits quantitatively, but Neusser reports an increase of eosinophiles and the presence of myelocytes in the blood.

Ritchie¹ confirms Neusser and found also the young leucocytes more numerous than normal.

<sup>&</sup>lt;sup>1</sup> Edin. Med. Journal. June. 1896.

Fehling, Sternberg, Chrobak found no increase of eosinophiles. Rieder's case was normal in all respects: Red cells, 4,892,000; white cells, 5,600; eosinophiles, 3.6 per cent; polymorphonuclear cells, 61 per cent.

Ewing says: "The usual condition of the blood in osteomalacia appears to be that of moderate secondary anæmia. The leucocytes have varied from subnormal to moderately increased numbers. The lymphocytes are usually very numerous, an excessive proportion (maximum 56 per cent) having been found by Tschistowitch. High normal proportions of eosins have been found by several observers, but not by others."

### RICKETS.

1. Anæmia is always present in severe cases and often in moderate ones. This, together with the fact that many cases of rickets are associated with an enlargement of the spleen, has led to the use of the misleading term "splenic anæmia." . There is no form of anæmia found in rickets that may not be found in other conditions (Morse).

Hock and Schlesinger found an average of 2,500,000 red cells in a considerable number of cases with and without enlarged spleen.

Von Jaksch describes a case in which the red cells sank from 1,600,000 to 750,000 within three months, and Luzet saw a similarly rapid process, the cells falling from 2,110,000 to 1,596,000 within three weeks. On the other hand, in Morse's admirable study of twenty well-marked cases the red cells averaged over 4,500,000 and not a case fell below 3,500,000.

2. The hæmoglobin is always relatively low; it averaged 63 per cent in Morse's cases, a color index of about .7. Felsenthal got similar results.

# White Corpuscles.

It is often difficult to say whether or not the leucocytes are increased, owing to the occurrence of most cases in infants at an age when leucocytes are always higher than in adults—how much higher at any given age depends largely upon the degree of vigor and forwardness of development of the individual child.

In Morse's series, for example, the average age of the infants is twelve months. And for this age none of the counts in his series

<sup>1</sup> Cited by Ritchie (loc. cit.).

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seem to me necessarily abnormal. They are all under 16,000 except three, these three being 17,900, 18,800, and 22,000 respectively, the latter in a nine months' infant. Many of the counts seem to me subnormal for infancy (5,500, 7,200). Most observers find leucocytosis present in many cases, but not in all.

### QUALITATIVE CHANGES.

### Red Cells.

As in all anæmias of infants, the "degenerative" and "regenerative" changes are relatively common.

Polychromatophilic forms and nucleated corpuscles are frequently to be found, the latter often in great numbers but with a majority of the normoblast type.

### White Cells.

Lymphocytosis is said to be marked, but, as with the question of leucocytosis, we are never quite sure whether the numbers are abnormal *for that age*, for lymphocytosis is the normal condition in infants' blood.

When, however, as in a case mentioned by Rieder, we find 75 lymphocytes in every 100 leucocytes, the child being four years old, we are surely dealing with a pathological condition. Another of his cases, a seven-months' child, rachitic, with 57 per cent of lymphocytes, seems to fall within normal limits. Not so with Morse's The highest percentage of lymphocytes in his series was 69, in an infant of two months. I have similar counts in health at that age. The average of his twenty cases is 43 per cent, which is, if anything, rather low for that age. The same difficulty arises with regard to the reports of eosinophilia in rickets, since eosinophiles are always relatively numerous in infancy. Morse's highest figure was 7 per cent his average 3 per cent. Hock and Schlesinger found 20 per cent in one subject, and Weiss 16 per cent in another. They were highest in cases with splenic tumor. In Rieder's four cases and in the three seen at the Massachusetts General Hospital. no eosinophilia was present. Myelocytes in small number (.5-.2 per cent) are not uncommon, and may be considerably more numerous.

# CHAPTER IX.

# BLOOD DESTRUCTION AND HEMORRHAGIC DIS-EASES.

### PURPURA HÆMORRHAGICA.

The blood is practically that of anæmia from hemorrhage (red cells and hæmoglobin reduced, white cells increased, occasional nucleated red corpuscles or polychromatophilic forms). Agello¹ has found methæmoglobin in the blood, and hence concludes that the disease is a poisoning of the corpuscles by ptomaïns absorbed from the intestine.

The blood plates are much diminished and may be entirely absent in the worst stages.

Bacteria of various kinds have been reported in the disease, but negative results are also common, and their presence is probably not significant.

The red cells may fall as low as 2,500,000, but are much oftener slightly or not at all diminished. In many mild cases there are no demonstrable blood changes. On the other hand, Osler mentions a case which sank to 1,800,000, and the loss of blood may give rise to a fatal anemia of the microcyte type (see page 154).

Bensaude<sup>2</sup> has observed that in 16 cases characterized by large hemorrhages (2 = acute "infectious," 2 with tuberculosis, 2 chronic, 10 = Werlhof's disease) the clot shows no retraction and no transudation of the serum. Cases with small hemorrhages (toxic, rheumatic, cachectic, and nervous) do not show any such abnormal characteristics. Hence he concludes that at the outset of a case of purpura, observation of the clotting process may enable us to fore-tell whether or not the case is to be of a serere or of a mild type. He found the blood lesion above described to be greatest during the hemorrhagic crises, slowly disappearing between them. Hayem has confirmed these observations. He finds the fibrin network almost invisible. Despite this and despite the absence of contraction

<sup>&</sup>lt;sup>1</sup> Riforma Med., Napoli, 1894, p. 103. <sup>9</sup> La Semaine Méd., 1897, p. 21.

in the clot, the actual rate of clotting is normal. Hayem has seen similar failure of contraction when the blood plates are plenty. It occasionally occurs in symptomatic purpura (e.g., from phthisis).

### SCURVY.

There are no characteristic blood changes known. When hemorrhage is severe the red cells may sink very low, to 557,875 in a case of Bouchut's; Ouskow and Hayem saw counts of 3,500,000 and 4,700,000. The usual qualitative changes of secondary anæmia are present in severe cases; hæmoglobin suffers as usual more than the count of red cells.

Leucocytes may be increased, whether from hemorrhage or from some complicating inflammatory process. This was not so in the following case of my series: January 26th—reds, 3,120,000; whites, 3,600; hæmoglobin, 40 per cent. January 29th—reds, 3,600,000, hæmoglobin, 55 per cent. Eight days later hæmoglobin 65 per cent.

"The red cells vary in number and size according to the length and severity of the disease. On account of the frequency of inflammatory complications and hemorrhages the leucocytes are usually increased, Uskow finding as high as 47,000. Litten, however, observed no leucocytosis, and the writer in two well-marked but uncomplicated cases found no increase" (Ewing).

Barlow's disease may lower the red cells as far as 976,000—as in a case of Reinert's—the hæmoglobin being 17 per cent. and the white cells 12,000. This was the day before death. The blood plates are not diminished, and the clot retracts normally.

#### HÆMOPHILIA.

The blood changes are practically those just described and show nothing characteristic of the disease. Coagulation is slower than normal and blood plates are sometimes very scanty. The white cells are sometimes persistently diminished, as in the following cases:

I.

	Sept. 11th.	Sept. 14th.	Sept. 17th.	Sept. 20th.	Sept. 23d.	Sept. 24th.
Red cells		3,400	3,800	3,900	3,700	3,800,000 3,300
Hæmoglobin	42 per cent.	••••	• • • •	••••	64 per cent.	49 per cent.

II.

February 8th. February 4,400,000 3,600, 5,000 3,600, 5,000 28 per cent. 28 per c	$\left.\begin{array}{c} 000\\ 000 \end{array}\right $ Daily nose-bleed.
----------------------------------------------------------------------------------	-------------------------------------------------------------------------

### BLOOD DESTRUCTION (HÆMOCYTOLYSIS).

- I. Besides the slow destruction of corpuscles which takes place in any ordinary anæmia, we have a group of conditions under which a large number of red cells are suddenly destroyed in the circulation itself. This may take place by—
- 1. Separation of the hæmoglobin from the corpuscles so that it colors the serum.
- 2. Actual breaking to pieces of the red cells without separation of the hæmoglobin.

If normal blood is drawn and left to stand, the serum which separates from the corpuscles is not red-tinged or but very slightly so, provided all shaking and jarring are avoided. A very slight reddish tinge may appear in the serum even with most careful technique. In some conditions the hæmoglobin, while not actually separated from the corpuscles within the vessels, is so loosely connected to them that a considerable quantity separates post mortem and colors the serum in spite of the avoidance of any jar.

This condition is to be distinguished from true hæmoglobinæmia, in which the serum is actually colored before leaving the vessels, although the two conditions really represent only different degrees of vulnerability of the red cells.

We are surer of a diagnosis of hæmoglobinæmia when we find bits of broken-down cells in the fresh blood and the additional evidence of hæmoglobinuria or jaundice.

- 1. Severe forms of malaria, yellow fever, typhus fever, severe forms of septicæmia, and rarely scarlet fever may cause hæmoglobinæmia. Also alcoholism with fever, nephritis, cirrhosis, grave icterus, quinine poisoning, and eclampsia (Hayem).
- 2. Paroxysmal hæmoglobinæmia, so-called, is a variety whose cause is unknown and which does not seem secondary to any other disease, unless a certain relationship to syphilis be established, and to malaria. The attacks are brought on by a great variety of causes (cold, muscular or mental strain, etc.). Some persons can always bring on an attack by putting the hand or foot into cold water.

### Blood Examination.

Coagulation is very rapid, but the clot soon dissolves again (Hayem). The fresh blood occasionally shows deformities in the corpuscles or bits of broken cells, and lack of rouleaux if examined during a paroxysm. As a rule the corpuscles of the peripheral blood look normal. Frazer has recently reported a case in which he excited a paroxysm by a cold bath, and studied the blood with great care.

Red cells.	White cells.	Per cent hæmoglobin.	Blood plates.
4,075,000	15,000	50	450,000
3,633,300	21,800	50	696,000
4,200,000	21,500	50	525,000 <b>4,250.000</b> (!)
3,800,000 4,100,000	$17,700 \\ 18,700$	50 · 50	1,600,000 500,000
	3,633,300 3,760,000 4,200,000	4,075,000     15,000       3,633,300     21,800       3,760,000     21,300       4,200,000     21,500       3,800,000     17,700	A,075,000   15,000   50   15,000   50   3,633,300   21,800   50   3,760,000   21,300   60   4,200,000   21,500   50   3,800,000   17,700   50

The enormous increase of "blood plates" is striking. It is difficult to resist the conclusion that these blood plates were bits of broken red corpuscles. The serum was currant-jelly colored. The appearance of the corpuscles was quite normal.

All that is known of the disease is expressed by saying that for *some reason* the red cells are abnormally *sensitive*, so that any one of a variety of slight disturbances is sufficient to separate their hæmoglobin and set it loose in the plasma.

- 3. Extensive burns have been reported to cause hæmoglobinæmia with breaking up of the red cells, presumably through changes in the serum similar to those which make duodenal ulcer so common a sequel to bad burns.
  - 4. Snake poison and scorpion poison may have similar effects.
- II. Another group of corpuscle destroyers is that which works by changing the *hæmoglobin* to *methæmoglobin*. The most important of these is—
- 1. Chlorate of Potash.—This destroys the corpuscles and produces hæmoglobinæmia and the usual train of symptoms (jaundice, dark urine, etc.) due to this.

Brandenburg<sup>1</sup> examined the blood of a woman who had taken <sup>1</sup> Berliner klin. Woch., 1895, No. 27.

two and one-half ounces of chlorate of potash in water the night before. The blood showed *marked* leucocytosis, broken and distorted red cells. In gross it was chocolate-colored and the serum after separation of the clot was brown. The red cells progressively decreased as follows:

	Red cells.	White cells.
First day	4,300,000	20,000
Second day	2,500,000	
Fourth day	2,300,000	
Fifth day	2,100,000	
Sixth day	1,900,000	
Seventh day	1,600,000	15,000 (death).

Jacob¹ studied a similar case: Thirty hours after a dose of  $25~\rm gm$  of KClO $_{\rm s}$  the blood showed: Red cells, 4,425,000; white cells, 80,000 (stained specimen resembles leukæmia). Next day, red cells, 1,825,000 (broken and decolorized); white cells, 60,800. Fourth day, red cells, 2,225,000; white cells, 14,000.

2. Ehrlich and Lindenthal <sup>2</sup> report the case of a patient who was poisoned with nitrobenzol. Ten hours after the blood was chocolate-colored and showed methæmoglobin bands. Under the microscope there were no changes till the third day, when poikilocytosis appeared.

	Red cells.	White cells.	Per cent hæmo- globin.	Nucleated red cells per cubic millimetre.
Fifth day Seventh day Eleventh day Fifteenth day Seventeenth day Nineteenth day " " death.	1,845,000 1,600,000 905,000	Much increased. """"""""""""""""""""""""""""""""""""	55 50 44 40 	2,070 7,900 24,700(!) 12,000 1,300 540

The nucleated red cells were at first mostly normoblasts; later mostly megaloblasts. Posselt <sup>3</sup> and Boas <sup>4</sup> have published similar cases.

3. Antipyrin and antifibrin in doses of from thirty to forty-five grains may cause great cyanosis and dangerous prostration

<sup>&</sup>lt;sup>1</sup>Berl. klin. Woch., 1897, No. 27.

<sup>&</sup>lt;sup>2</sup> Zeit. f. klin. Med., 1896, p. 427.

<sup>&</sup>lt;sup>3</sup> Wien. klin. Woch., 1897, No. 30.

<sup>&</sup>lt;sup>4</sup> Deut. med. Woch., 1897, No. 51.

through the transformation of the hæmoglobin and methæmoglobin. In certain persons, even much smaller doses produce the same effect.

- 4. Phenacetin poisoning (Kronig: Berl. klin. Woch., 1895) may cause actual blood destruction with anemia in case the patient survives the immediate effects of the deprivation of oxygen. A fatal case of chloral poisoning at the Massachusetts General Hospital showed 14,400 leucocytes with 54 per cent of hæmoglobin.
  - 5. Phosphorus poisoning (see Liver, page 311).
- 6. Workers in aniline dyes and nitroglycerine factories may be severely poisoned by *nitrobenzol* compounds inhaled and producing methæmoglobinæmia.
- 7. Pyrogallic acid and pyrogallol as used in treatment of skin diseases may lead to death through destruction of the red cells. Chromic acid (for instance, as applied through the vagina) may have a similar effect.

Many other less common substances work the same ill effects on the blood.

- III. A third group of substances, of which *earbonic oxide gas* is the type, poison by combining chemically with the hæmoglobin and preventing its combination with the oxygen of the air.
- 1. Illuminating gas is for our purposes the most important of this group.

The appearance of individual blood cells is not altered nor do they break up, but the corpuscles are useless to breathe with, as they cannot take up oxygen.

The color of the blood is very bright red, much brighter than normal.

### Red Cells.

Von Limbeck' found in two cases 6,630,000 and 5,700,000 respectively. The *volume* of these corpuscles (estimated by Bleibtreu's method) was greatly increased, amounting to 70.7 per cent (normal, 41–48 per cent), so that apparently the size of the individual cells is increased.

Münzer and Palma<sup>2</sup> found 5,700,000 red cells in one case.

Ehrlich found numerous normoblasts in one case.

<sup>&</sup>lt;sup>1</sup> Loc. cit., p. 234.

<sup>&</sup>lt;sup>2</sup> Zeit. f. Heilk., vol. xv., p. 1.

### Leucocytes.

Eaton¹ reported four cases, in all of which the white cells were increased, the counts ranging between 15,000 and 22,000 per cubic millimetre.

Münzer and Palma (*loc. cit.*) found 13,300 in their case. Twenty-four such cases have been examined at the Massachusetts General Hospital with the following results:

TABLE LIX.—ILLUMINATING GAS POISONING.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
41	M.		31,200		Coma; recovery.
49	M.		27,100		September 12th; coma.
			19,900		September 13th, entirely well.
21	M.		26,000	70	Coma; recovery.
19	M.		25,470	97	
50			25,200		
40	M.		22,900	75	
			21,200		November 27th; coma.
			15,500		November 29th; convalescent.
Adult.			22,000		Recovery.
60	M.		20,400	75	Coma; recovery.
25	M.		20,360	110	Death.
45	M.		20,100		Coma; death.
Adult.			20,000		
64			19,600	80	
24			18,800		
16	F.		18,500	84	Coma; recovery.
27			18,100		
50			17,300	90	Temperature, 101°; recovery.
22			17,100		
19	M.		17,000		December 22d.
	1		17,500		December 23d.
		4,930,000	17,000		
56			15,600		
21			15,000	80	
55			12,000	60	
28			9,400		
33			9,300	73	
20			6,700	58	

Warthen 2 reports the same condition in a single case. Here the specific gravity was also very high (v. Limbeck finds that this is to be explained by the increase in the actual size of the corpuscles).

<sup>&</sup>lt;sup>1</sup> Boston Medical and Surgical Journal, March 14th, 1895.

<sup>&</sup>lt;sup>2</sup> Virchow's Archiv, vol. exxxvi.

When there is any doubt as to diagnosis, the following test will settle it: Shake a small quantity of fresh-drawn blood into three times its volume of subacetate of lead. If the blood contains CO the mixture becomes of a fine red color; otherwise it turns chocolate-colored.

2. Da Costa (*Med. News*, March 2, 1895) reported a considerable diminution in hæmoglobins of patients during *etherization*, especially anæmic patients, but the investigations of Lerber<sup>2</sup> do not confirm this.

Tansy Poisoning.—A single case examined at the Massachusetts General Hospital showed: Red cells, 4,600,000; white cells, 21,-000; hæmoglobin, 70 per cent.

Corrosive Poisoning (Ammonia Fumes).—A patient whose throat was covered with a fibrinous pseudo-membrane in consequence of inhaling ammonia fumes showed a leucocytosis of 25,800. Red cells and hæmoglobin normal. Another with vomiting and purging gave a count of 20,700 white cells.

### AMMONIA.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
24			27,000		Mouth and pneumonia.

Opium Poisoning (Chronic).—The majority of cases of the morphine habit show normal blood, but in October, 1897, a man of twenty-six entered the Massachusetts General Hospital for the morphine habit who showed at entrance 36,000 leucocytes per cubic millimetre. Five days later the count was 21,200. A differential count of 500 leucocytes made on this day showed: Polymorphonuclear neutrophiles, 71 per cent; small lymphocytes, 12; large lymphocytes, 10; eosinophiles, 6; myelocytes, 1. At the time of leaving the hospital he still showed a leucocytosis of 16,400. He had no fever, and the physical examination was entirely negative.

Ptomain Poisoning (Rotten Fish).—A mother and her four children were brought to the Massachusetts General Hospital suffering

<sup>&</sup>lt;sup>1</sup> Rubner: Zeit. f. anal. Chemie, xxx., p. 112.

<sup>&</sup>lt;sup>9</sup> Inaug. Dissert., Basel, 1896 (see p. 109).

from the effects of decayed fish eaten that day. The blood showed the following: (1) mother: leucocytes, 21,600, of which 95.3 per cent were polymorphonuclear; (2) boy of seven years: leucocytes, 19,900; (3) boy of three years: leucocytes, 56,800, of which 92 per cent were polymorphonuclear; (4) girl of five years: leucocytes, 32,600; (5) girl of thirteen months: leucocytes, 55,400. The red cells and hæmoglobin were normal. All the patients made prompt recoveries.

### Corrosive Poisoning.

### Carbolic Acid.

Age.	sex.	Red cells.	White cells.	Per cent hæmoglobin.	Remarks.
27 23	••		10,300 15,200		No signs.

### ARSENIC.

66	 	11,600		

### ACUTE ALCOHOLISM.

It has been shown experimentally that in animals made drunk with alcohol, there is an invasion of the blood and tissues by microorganisms from the intestine. It may be that some of the counts here recorded are thus to be explained.

TABLE LX.—ACUTE ALCOHOLISM.

Age.	sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
31			44,000	95	
			32,000		2d.
			20,000		3d.
27			42,000	. ,	Followed by delirium tremens.
50			29,800		Autopsy.
			25,000		Delirium tremens.
35			23,900		
36	F.		15,900		Two weeks drinking hard:
90	1.		10,000	• •	Temperature 102°; died. delirium tremens.
38	M.		14,200	74	Temperature 101°.

Table LX.—Acute Alcoholism (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
42	М.		12,000	62	Temperature 101°; delirium tremens.
42 46			$12,600 \\ 11,000$		Chronic case delirium tremens.
			10,200	• • • • • • • • • • • • • • • • • • • •	Delirium tremens.
32	М.	3,936,000	10,200	30 (?)	
44	М.		9,600	80	
			8,100		
29	F.	4,288,000	8,000	55	Delirium tremens.
37	M.		7,800	62	
60	F.		7.450	65	
00	1.		7,000		December 21st.
			11,900		December 26th.
				• •	December zoth.
• •			6,800		D 11 1
			6,400		Delirium tremens.
32	M.		5,700	68	Autopsy.
28	M.		5,600		Delirium tremens.
			5,600		

### PLUMBISM.

Among the deleterious effects produced by lead in the human body, anæmia is one of the most serious. It is of the type of ordinary symptomatic anæmias except in one particular to which attention has recently been called by Grawitz, viz., spotting or stippling of the red cells with fine basophilic granules, which can be well seen in specimens fixed in absolute alcohol for a few minutes and stained with Loeffler blue, Goldhorn's polychrome, methylene blue, or other basic dyes. These basophilic granules are often seen in various forms of very severe anæmia, but in plumbism they appear even when the anæmia is otherwise of a mild type.

The following table exemplifies the degree of anæmia ordinarily seen:

TABLE LXI.—LEAD POISONING.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
29 30		4,500,000 3,800,000	23,400 22,800	50 48	Lead colic and headache.
38 21		5,130,000	16.800 $22,700$ $14,800$	64 59	Eighth day.

TABLE LXI.—LEAD POISONING (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
40			14,600 11,400	••	December 28th. February 2d. Polynuclear, '71.2 per cent. Lymphocytes, 24.6 " Eosinophiles, 4.0 "
21 44 35 17 33		3,888,000 3,700,000 3,820,000 4,258,000	12,600 11,600 10,000 9,200 8,600	72 38 50 48 55	Myelocytes, .2 " Fits, colic, anæmia. Colic. Chronic.
32 52		3,208,000 4,221,000	7,200 7,100	50 45	August 10th. Polynuclear, 72.4 per cent. Lymphocytes, 23.3 " Eosinophiles, 2.5 " Myelocytes, 1.8 " Megaloblasts, 1. Normoblasts, 1.
		4,848,000	8,000	50	August 20th. Polynuclear, 71.4 per cent. Lymphocytes, 25.6 " Eosinophiles, 2.6 " Myelocytes, 4 " Normoblasts, 1.
33 44 40		4,000,000 3,056,000	5,200 5,200 4,500	50 45	

## SUNSTROKE AND HEAT EXHAUSTION.

The leucocyte count may be either high or normal, according to conditions not well understood.

### SUNSTROKE.

Age.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
10 35		24,000 13,400 22,800	67	Two days later. Temp., 107°. Died.
45 23		21,000 10,000		Temp., 110°, first day.
47 50		$\begin{array}{c c} 5,200 \\ 10,000 \\ 10,000 \end{array}$	95	Temp., 104°, fourth day. Died.
32		9,800	62	

### HEAT EXHAUSTION.

Age.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
62  34 54		24,000 18,200 11,000 9,000 5,000	80 75 .:	Recovery. Recovery. Recovery. Recovery. Recovery. Temp., 98.8°. Temp., 98°. Temp., 99°.

# ELECTRIC SHOCK.

Age.	White cells.
25	 8,900
24	

# PART VI.

# MALIGNANT DISEASE, BLOOD PARASITES, AND INTESTINAL PARASITES.

## CHAPTER X.

### MALIGNANT DISEASE.

### THE BLOOD AS A WHOLE.

- 1. The specific gravity is reduced in most cases, running roughly parallel with the hæmoglobin.
- 2. Coagulation is normal or slower than normal in uncomplicated cases. When sloughing and inflammation are present it may be rapid.
- 3. Fibrin is usually normal; an increase means inflammation in or around the tumor or an inflammatory complication.
- 4. Occasionally the resistance of the red cells is extraordinarily low. In one of my cases the ordinary manipulations of preparing specimens (either fresh or film) for examination invariably mangled the red cells beyond recognition, no matter how quickly and carefully the technique was carried out. In the fresh specimen the red cells seemed to fuse into each other in clumps, their biconcavity lost. The plasma became turbid with hæmoglobin despite every precaution.

This was a case of cancer of the kidney with multiple hæmorrhage from various surfaces. I have never seen another case like this one, but in literature several such are mentioned.

#### CANCER.

# Red Corpuscles.

As in tuberculosis, we are frequently surprised to find but little diminution in the number of red cells. In all but very advanced

cases this is the rule. It is a change of the individual red cells (pallor, loss of size, of weight, degenerative changes), rather than a reduction of numbers.

Nevertheless in the later cachetic stages of most cases of malignant disease, we do find a quantitative anæmia, the counts often running as low as 2,500,000 and occasionally sinking as low as in pernicious anæmia. Thus v. Limbeck records a case (complicated by repeated hemorrhages) with only 950,000 red cells per cubic millimetre. The lowest of my own cases was 1,457,000 per cubic millimetre.

There seems to be no considerable difference between cancer and sarcoma as regards their effect on the red cells. The following table summarizes our cases:

# TABLE LXII., A.—GASTRIC CANCER.

# Red cells. Between 1,000,000 and 2,000,000 6 cases. " 2,000,000 " 3,000,000 17 " " 3,000,000 " 4,000,000 37 " " 4,000,000 " 5,000,000 29 " " 5,000,000 " 6,000,000 21 " Over 6,000,000 4 "

Average, 4,090,000 + 114 cases.

Nucleated red cells present in 11 cases out of 114 examined. Normoblasts always in majority. A few megaloblasts in 3 cases.

### TABLE LXII., B.—GASTRIC CANCER.

Leucocytes	per cubic	millimetre.	
Between	3,000 and	4,000	1 case.
66	4,000 "	5,000	4 cases
*64	5,000 "	6,000	17 "
66	6,000 "	7,000	9 "
66	7,000 "	8,000	8 "
66	8,000 "	9,000	8 "
66	9,000 "	10,000	9 "
66	10,000 "	12,000	6 "
46	12,000 "	15,000	4 "
66	15,000 "	20,000	12 "
66	20,000 "	30,000	
44	30,000 "	40,000	

Total, 167 counts in 86 cases.

Average, 10,600+

Fifty-six additional cases give the following counts:

3,000 to 4,000 = 1 4,000 " 5,000 = 4 5,000 " 6,000 = 7 6,000 " 7,000 = 14 7,000 " 8,000 = 10 8,000 " 9,000 = 10 9,000 " 10,000 = 15 10,000 " 12,000 = 21 12,000 " 15,000 = 14 15,000 " 20,000 = 14 20,000 " 30,000 = 3 30,000 " 40,000 = 2

115 counts.

As will be seen by consulting Table LXII., A, the count of red cells is sometimes above normal, doubtless due to concentration of the blood from some cause. Probably the same influence is at work in other cases, and many of those showing normal counts have really fewer red cells than they should. Such abnormally high counts are not rare, as the following examples show:

Author.	Case.	Affection.	Red cells.	Per cent hæmoglobin.
Osterspey 1		Cancer of the stomach		80
Osterspey		Cancer of the liver and stomach	-6,184,000	87
Osterspey	3	Cancer of the gullet	8,280,000	48
Neubert 2	1	Cancer of the stomach	5,085,000	73
Neubert	2	Cancer of the liver	4,918,000	70
Reinert 3		Cancer of the stomach	6,200,000	77

I wish to lay some stress upon this point, because it has been stated by some recent writers (e.g., Grawitz: "Pathologie des Blutes," Berlin, 1896) that the red cells are almost always diminished in malignant disease.

The high counts in cancer of the gullet are obviously to be explained by the lack of liquid taken, the blood being greatly concentrated as in any other form of starvation.

That this increase is not invariably present (see Table LXIII., page 384) is doubtless because some esophageal tumors permit the

Dissert., Berlin, 1892.
 <sup>2</sup> Inaug. Dissert., Dorpat, 1889.
 <sup>3</sup> "Zählung d. Blutkörp.," Leipzig, 1891.

ingestion of liquid in normal amounts and of a certain amount of solids. In gastric cancer high counts are usually due to concentration of the blood produced by vomiting or to the lack of absorption of fluid accumulating in a dilated stomach with pyloric obstruction.

The highest counts in the Massachusetts General Hospital series are in simple gastric cancer without any stenosis at either end of the organs, and the lowest count (1,632,000) was in a similar case just before death. Taking all the cases of cancer in this series together, the average of the seventy-five cases at the time when treatment began was 4,140,000 red cells per cubic millimetre.

In Osler and McCrae's 59 cases the average red count was 3,712,-186 per cubic millimetre. Their counts ranged:

Over 6,000,	000	3 cases.
5,000,000 to	6,000,000	17 44.
4,000,000 "	5,000,000	17 "
3,000,000 "	4,000,000	16 "
2,000,000 "	3,000,000	8 "
1,000,000 "	2,000,000	8 "

# Hlpha moglobin.

Bierfreund, who has examined seventy-two cases with regard to their percentage of coloring matter, found that in relatively slow and long-standing cases it averaged 68.5 per cent, and in the worst cases 57.5 per cent. In cases of mammary cancer after operation the hæmoglobin is of course lower owing to hemorrhage, and Bierfreund noticed that as a rule the hæmoglobin began to rise toward normal much later than after operations for non-malignant conditions—a week later on the average—and that it never reached the point at which it was before the operation.<sup>2</sup>

The following table from Bierfreund is of interest as illustrating these points. Cases were examined before and after operation, and the examinations were continued daily after the operation until the hæmoglobin began to rise again. This occurred very late as compared with other operations.

<sup>&</sup>lt;sup>1</sup> Langenbeck's Archiv, vol. xli.

<sup>&</sup>lt;sup>2</sup> This is all the more extraordinary because Bierfreund specially noted that even in patients who gained weight notably after the operation the hæmoglobin did not rise so high as it had been before operation; he watched them for months after it. Apparently the actual presence of the tumors is not the only cause of the lack of corpuscle substance.

Diagnosis.	Per cent hæmoglobin before operation.	Per cent hæmoglobin after operation.	Per cent loss.	Regeneration time.
Malignant tumor without complication.	68.5	53	15.5	23 days.
Very large or rapidly growing tumors.	56.6	38.4	18.2	27.8 days.
Tumors with "softening" or disturbances of function.	57.5	39.7	17.8	27 days.
Total, 72 cases.	Av., 60	Av., 42.8	17.2	Av., 25.9 days.

By "regeneration time" is meant the number of days elapsed after operation before the hæmoglobin begins to rise. After operations for other causes (non-malignant) the average regeneration time is fourteen to twenty days.

It is very important that these results of Bierfreund's should be tested. In Mikulicz's surgical clinic at Breslau all patients have their hæmoglobin tested regularly. Osler and McCrae in 52 cases of gastric cancer record an average of 49.9 per cent of hæmoglobin—a color index of .63. Their readings were:

Cases.	Cases.
80 per cent or more 3	40 " 50 8
70 to 80	30 " 40
60 " 70 6	20 " 30 7
50 " 60 5	Below 20 2

Reinbach<sup>1</sup> examined 16 cases and found the hæmoglobin range between 18 to 70 per cent, with an average of 50 per cent.

Rieder's cases average 53 per cent (sarcoma much lower—see below).

Laker<sup>3</sup> noticed the low hæmoglobin percentage in malignant tumors and thought it a help in excluding benign tumors or tuberculosis, in which the hæmoglobin is much less diminished.

In the 87 cases of malignant tumors in which I have notes of the hæmoglobin (see tables) the average is 58 per cent. Comparing this with the average count of red cells (4,140,000), we get a color index of .65, distinctly higher than the average of chlorotic cases, of which, however, the figures distinctly remind us. The highest cases

<sup>&</sup>lt;sup>1</sup> Langenbeck's Archiv, 1893, p. 486.

<sup>&</sup>lt;sup>2</sup> "Beiträge z. Kenntniss d. Leucocytosis," Leipzig, 1892 (Vogel).

<sup>&</sup>lt;sup>3</sup> Wien. med. Woch., 1886, Nos. 18 and 19.

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of this series had 100 per cent and 90 per cent of hæmoglobin respectively, and the lowest 20 per cent and 22 per cent; in these last two cases the color indexes were .36 and .58 respectively, not excessively low. As pointed out by Taylor (loc. cit.), cases of malignant disease can be divided into three groups with reference to their blood:

- 1. Those with approximately normal blood.
- 2. Those with a low hæmoglobin but a nearly normal number of cells.
- 3. Those with great diminution both in cells and coloring matter.

Among our own cases at the Massachusetts General Hospital about one-half fall under the second group, one-quarter under the first, and one-quarter under the third.

As the disease progresses, the red cells and hæmoglobin steadily go down (except in cancer of the gullet), and at the time of death 1,000,000 cells per cubic millimetre is not rare. It is very rare to find the red cells reduced below 1,000,000, much rarer than in pernicious anæmia. Improvement under treatment is rare in cancer, common in pernicious anæmia. This is important in diagnosis.

The color index usually remains below 1. Compared to most other varieties of secondary anæmia (e.g., those in tuberculosis or nephritis), a quantitative anæmia—that is, a loss of red cells as well as of hæmoglobin—is relatively more frequent. In general the degree of anæmia is parallel to the amount of cachexia, except when hemorrhage increases it (as in tumors of the stomach or uterus).

How far the anæmia may be due to actual destruction of cells by toxic (?) products of the tumors is doubtful. Grawitz found that the injection of extracts of cancerous tissues caused in rabbits a temporary dilution of the blood, so that the cells per cubic millimetre were diminished, and it may be that this plays some part in the causation of the low blood counts.

# Qualitative Changes.

(a) The average diameter of the red cells is often diminished either (as in chlorosis) by a diminution of the size of nearly every corpuscle, or by a less general shrinkage, many cells being of normal size. The very large forms seen in pernicious anæmia are rare in the anæmia of malignant disease, and never, I think, reach the size of the

giant forms seen in the former condition. Very small cells, on the other hand, are as common in advanced cases as in any other form of anæmia, except chlorosis. Deformities and degenerative changes are very common in well-marked cases, often as great as in pernicious anæmia, though they may be slight or absent.

According to Strauer, the *deformities* found in malignant disease are greater than those found in any form of tuberculosis, and this fact he thinks of value in diagnosis. This observation has been confirmed by Taylor.

Degenerative changes are sometimes well marked, but seldom, if ever, reach so extreme a condition as occurs in many cases of pernicious anæmia.

(b) Nucleated red corpuscles are the rule in all advanced cases, and in some others. Taylor found them in one-half of the twenty-two cases examined by him. Malignant disease differs in this respect from tuberculosis and most other conditions involving secondary anæmia, in that the nucleated red cells are much more common in cancer and may appear even when there is no considerable loss of red cells (numerically) or even when the hæmoglobin is also normal (Schreiber). I have found them in four-fifths of all severe cases examined.

As a rule the nucleated corpuscles are of the normoblast types (including small forms with dividing nuclei), but in very cachectic cases we may find megaloblasts as well—always, so far as I know, fewer in number than the normoblasts. Osler and McCrae found no typical megaloblasts in their 59 cases. The megaloblasts, when present, are in the minority as compared with the normoblasts. For example:

Case I. { Five normoblasts. Three megaloblasts. } Seen while counting 400 leucocytes.

Case II. { Two normoblasts. No megaloblasts. } Seen while counting 500 cells.

Case III. { Five normoblasts. No megaloblasts. } Seen while counting 200 cells.

Cases could easily be multiplied.

The characteristics of the blood changes in malignant disease, then, so far as concerns the red cells, are those of secondary anæmia, which at times attains the severest type—but only when cachexia is marked, or when hemorrhage complicates the disease.

The specific gravity follows in a general way the hæmoglobin percentage.

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On the *white corpuscles* in malignant disease a great deal of interest has centred, and very conflicting reports have been published. As the effects of cancer and sarcoma seem to be somewhat different, we will consider them separately.

### 1. THE LEUCOCYTES IN CANCER.

# (a) Quantitative Changes.

We should expect great differences in the blood of different cases if we consider what a wide range is included between the small, hard, slow-growing, curable cancer of the lip which may produce little or no impairment of the general health, and the "fulminating," rapidly growing cases with numerous metastases and profound prostration.

The former class of cases may show a blood normal in all respects, including a normal leucocyte count; while in the latter the blood may be so profoundly altered as to be confused with that of pernicious anæmia on the one hand, or with that of leukæmia on the other.

In a general way it may be said that the more "malignant" the cases the greater the changes in the blood.

The effect upon the leucocytes depends upon the following conditions:

- 1. The position of the tumor.
- 2. Its size, rapidity of growth, and the number, size, and position of its metastases.
  - 3. The resisting power of the individual.
- 1. Position.—(a) Tumors of the gullet involving stricture but not extending to other tissues are often accompanied by a diminution of the leucocyte count, owing to the starvation which they produce. This is not true of all cases, as is shown in the accompanying tables, but when the leucocytes are increased there is usually an involvement of other organs as well.
- (b) Cancers of the uterus and some of those of the stomach, by reason of the hemorrhage which they produce, are apt to be associated with a very high leucocyte count.
- (c) Tumors of the thyroid and of the pancreas are said by some writers to cause a specially great leucocytosis. In my own experience, tumors of the kidney have shown very marked increase of white cells.

2. Size.—Other things being equal, the larger and more rapidly growing tumors show in most cases a greater leucocytosis than small, slow-growing ones.

Thus the cancers of the lip and of the pylorus, scirrhus of the breast or of the penis, show smaller counts than tumors of the liver, omentum, and kidney, which are apt to grow more rapidly. Metastases in the bone marrow are thought by some observers to give peculiar qualitative blood changes (see below).

In general, metastases, being a method of rapid growth, simply add to the leucocyte count.

These distinctions eliminate some of the apparent contradictions between the findings of different individuals who were simply describing cancers of different types. But even within a single type, there are very marked differences in different cases. For instance, Alexander' found the leucocyte count in cases of scirrhus of the breast to vary between 2,360 and 21,700. Similar differences have been reported in cancers of the stomach (e.g., Schneider's finding leucocytosis in all of twelve cases, while Osterspey's in another series of twelve cases found leucocytosis in only two).

3. Resisting Power.—Possibly a part of these differences is to be explained by differences in the resisting power of the individual. But if this is so, we cannot measure the endurance of a given patient by his general health. As in the Civil War the pale, city-bred men outlasted the healthy farmers, so here the tumor's rapidity of growth seems often to be greatest in the most vigorous young individuals, while dried-up old women will resist its advance for a longer period.

We come now to the conditions to be found in particular types of cancerous growth.

Surprisingly little work has been done on the blood in malignant disease, such cases usually being under the charge of surgeons who rarely value such investigations. Except for scattered counts here and there, all our knowledge of the corpuscles rests on the work of Hayem and Alexander in France, and Rieder, v. Limbeck, Pée, Sadler, Reinbach, Osterspey, Grawitz, Strauer, Schneyer, and Schneider in Germany.

<sup>&</sup>lt;sup>1</sup> Alexander: Thèse de Paris, 1887.

<sup>&</sup>lt;sup>9</sup>Inaug. Dissert., Berlin, 1888.

<sup>&</sup>lt;sup>3</sup> Inaug. Dissert., Berlin, 1892.

### CANCER OF THE BREAST.

Most of our data come from Hayem¹ and his pupil Alexander.2

1. Scirrhus Growths.—Number of cases, 14. Average leucocyte count, 11,400. Highest count, 21,700; lowest, 2,360—the last is somewhat doubtful as to diagnosis; except for this case, which was in a very old, dried-up woman, the lowest count was 7,400.

In 10 out of the 14 cases, the count was over 10,000. In the 3 cases seen by the writer 2 showed no leucocytosis, 1 a considerable leucocytosis.

2. Medullary (Encephaloid) Growths.—Three cases, all over 10,000—average 11,300.

# Effects of Operation.

The following figures from Hayem are also of interest: Case I.—Scirrhus of the Breast.

Before operation.....

We Ser

Five weeks after operation (wound not quite

healed)	
ound completely healed 6,200	
ven months after operation	to rise again)
The growth recurred some months later and leucocytosis was	, ,
·	again present.
Case II.—Scirrhus of the Breast.	
	Second
** <del>***</del>	count.
Before operation	1,450
After operation	6,200
O TIT O' 1 CH T	
Case III.—Scirrhus of the Breast.	
	Second count.
	2,400
	2,400
After operation 8,400	
Case IV.—Scirrhus of the Breast.	
Before operation	7.400
After operation	
True operation	1,000
Case V.—Medullary Cancer of the Breast.	
Before operation 1	0,000
	9,000
	,
Hayem considers that by watching the leucocyte c	ount we can

Hayem: "Du Sang," Paris, 1889, p. 947.
 G. Alexander: "De la Leucocytosis dans les Cancers," Paris Thesis, 1887.

predict the coming of a recurrence before any physical signs are present. This he did in Case I. of the series just given.

I have seen no confirmation or refutation of this statement. It is one of the many points to which the attention of surgeons should be directed.

### CANCER OF THE STOMACH.

Here we have a much larger body of data to judge from. Thus: Hayem' in 12 cases found leucocytosis present in 5, absent in 7. Schneider<sup>2</sup> in 12 cases found leucocytosis in 12 (all).

Schneyer<sup>3</sup> in 18 cases found leucocytosis in 4, and these 4 all under 11,000.

Osterspey<sup>4</sup> in 12 cases found leucocytosis in 5.

Rieder in 6 cases found leucocytosis in 3.

Sadler<sup>5</sup> in 13 cases found leucocytosis in 2, and in both there were complications (abscess of liver, perforation of gullet with gangrene) to which the leucocytosis might be due.

Reinbach <sup>6</sup> in 4 cases found leucocytosis in 2.

Reinert in 2 cases found leucocytosis in 2.

Laache<sup>8</sup> in 5 cases found leucocytosis in none.<sup>9</sup>

Despite these facts we have the record of a certain number of single cases in which the leucocytosis has been enormous. For instance, Welch in Pepper's "System of Medicine" mentioned a case in which the ratio of white to red cells was 1:25 (normally  $1:750~\pm$ ). Eisenlohr's<sup>10</sup> case showed 1 white to 50 red, and Potain's<sup>11</sup> case showed 1 white to 48 red cells.

The Massachusetts General Hospital series of 86 cases showed leucocytosis in 30 cases and none in 56 (see Table LXII., B). Out of those showing leucocytosis 60 were under 12,500, that is, the leucocytes were but slightly increased, leaving only 20 out of 86 (or twenty-three per cent) in which the leucocytosis was very marked.

<sup>&</sup>lt;sup>1</sup> "Du Sang," Paris, 1889, p. 948. 
<sup>2</sup> Inaug. Dissert., Berlin, 1888.

<sup>&</sup>lt;sup>3</sup> Inaug. Dissert., Berlin, 1892. <sup>4</sup> Loc. cit.

<sup>&</sup>lt;sup>5</sup> "Original-Mittheilungen aus der Klinik v. Jaksch," 1891.

<sup>&</sup>lt;sup>6</sup> Langenbeck's Archiv, 1893, p. 486. <sup>7</sup> Loc. cit.

<sup>&</sup>lt;sup>8</sup> "Die Anämie," Christiania, 1883.

<sup>&</sup>lt;sup>9</sup> Apparently, since he draws attention to the fact that there is leucocytosis in a case of cancer of the uterus.

<sup>10</sup> Deut. Arch. f. klin. Med., 1877, vol. xx.

<sup>&</sup>lt;sup>11</sup> Gaz. des Hôp., 1888, No. 57.

Among these 20, the highest counts were 40,000 and 39,000, and the highest ratio 1:62.

In this series I have excluded all cases in which there was evidence of metastasis in other organs; this means excluding 7 cases, 6 of which showed leucocytosis, and helps to account for the low average leucocyte count in the other 86 cases.

In over three-fourths of these cases the diagnosis was made certain either by operation or by autopsy; all the others showed either a palpable tumor in old cachectic patients with pain and vomiting, or other equally clear evidence for the diagnosis. Doubtful cases have been excluded. As will be seen by the table, in some of the cases the counts were verified by repeated examinations, while in others only a single count—that made when the patient entered the hospital—was recorded.

As a rule, the high leucocyte counts were in the more cachectic cases; but this does not always hold. Three cases in Table LXII., A, were very cachectic but showed no leucocytosis.

The position of the tumor in one or another part of the stomach seemed to have no connection with the number of leucocytes. Osler and McCrae found no leucocytosis in 29 cases out of 62. Their counts showed:

### LEUCOCYTES.

Belov	v 5	6,000										 				 				14	cases.
5,000	to	8,000				٠			 			 								15	66
8,000	46	12,000					 					 		3		 				15	64
12,000	66	20,000				2		٠.								 	٠			15	66
20,000	66	30,000										 	b			 				3	44
																				_	
																				62	cases.

Their highest count, 28,000, was in a case with extensive hepatic metastasis. The number seemed to bear no fixed relation to the situation of the growth, nor to the amount of ulceration, of metastasis, or of fever.

On the whole, leucocytosis is relatively infrequent in cancer of the stomach, occurring in only about one-third of the early cases. As the disease progresses we may get a leucocytosis, particularly in case its growth is *rapid* and metastases are frequent and numerous; but some cases, particularly those in which the tumor is small and grows slowly, may run their entire course without any leucocytosis being present. In this respect they are like the majority of small, slow-growing cancers in other parts of the body (see below).

Hemorrhage or perforation is of course accompanied by an increase in the number of white cells—in fact the highest count in the present series (105,600) occurred in a case in which a cancer of the stomach with metastases in the liver perforated into the peritoneal cavity and started a virulent, quickly fatal peritonitis.

### DIGESTION LEUCOCYTOSIS IN CANCER OF THE STOMACH.

A considerable body of statistics has accumulated to show that in the great majority of cases of gastric cancer the leucocytosis of digestion (see above, page 98) does not occur. R. Müller¹ noticed this fact in 5 cases of cancer of the stomach. Schneyer² in 18 cases found it invariably absent, while in 3 cases of benign stenosis of the pylorus a considerable digestion leucocytosis appeared, as was also the case in 7 out of 8 cases of ulcer of the stomach, the exception being a fatal case.

He found both incipient and advanced cases to be similarly affected. In 5 of his cases and in some of Müller's HCl was present in the gastric contents, so that the absence of digestion leucocytosis was not due to absence of HCl.

Hartung<sup>3</sup> in a series of 10 cases (mostly advanced) found no digestion leucocytosis, whereas a marked increase occurred in cases of malignant disease of other organs. Osler and McCrae found no digestion leucocytosis in 12 out of 22 cases.

Capps' in 17 cases examined at the Massachusetts General Hospital found a digestion leucocytosis in 2, the increase being respectively 3,270 and 3,850 cells over the count before the beginning of digestion. In the other 15 cases there was no increase after a large proteid meal. Since Dr. Capps' article 20 more cases have been investigated at the hospital, in 19 of which the digestion leucocytosis was absent. Thus in a total of 37 cases only 3, or eight percent, showed any digestion leucocytosis. In 5 out of 10 cases of chronic gastric catarrh the digestion leucocytosis was present; it was also present in a case of benign stricture of the pylorus in a man of forty-nine on whom an operation was successfully performed

<sup>&</sup>lt;sup>1</sup> Prag. med. Woch., 1890, No. 17.

<sup>&</sup>lt;sup>2</sup> Zeit. f. klin. Med., 1895, p. 475.

<sup>&</sup>lt;sup>3</sup> Wiener klin. Woch., p. 697, 1895.

<sup>&</sup>lt;sup>4</sup> Boston Med. and Surg. Journal, November 4th, 1897.

later. The digestion leucocytosis may, however, be absent in simple debility. On the whole, it seems of little diagnostic value.

Three cases of ulcer of the stomach showed marked increase, as did several cases of hyperacidity and other gastric disorders (see Diseases of the Stomach, page 300).

### CANCER OF THE STOMACH WITH METASTASES.

Most writers have not separated the cases with metastasis from those without it. A glance at the 13 cases of Table LXII., C, shows that with one exception leucocytosis was present throughout most of the disease.

TABLE LXII., C.—CANCER OF THE STOMACH WITH METASTASES.

-						
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	54		5,539,000	3,900 a.c.	35	Polynuclear, 65 per cent.
			, ,	4,200 p.c		Lymphocytes, 32 "
	40	3.5		~		Eosinophiles, 3 "
2	48	M.	4,228,000	5,000	70	January 23d. Stomach and liver.
				6,200		January 28th, mealtime.
				7,300		January 28th, three hours later.
3	66	M.		7,000	70	February 14th, no cachexia.
		112.	5,168,030	14,400	62	March 6th, liver involved.
		k	0,100,000	19,600		March 12th.
				21,640		March 17th, cachectic.
4	56			8,000	85	Operated.
				8,500 a.c.		
				7,600 p.c.		
5	45		3,536,000	8,100	60	
6	23		3,120,000	9,000	20	Operation.
				19,000		Two weeks later. Died.
7	60			15,000	60	+ Liver.
8	Adult.	М.	3,352,000	16,000	::	Stomach, liver, and spleen.
9	44	::	4,128,000	17,100	40	+ Liver.
10	54	М.	4,160,000	24,000	60	Stomach and liver.
				24,200		
11	4194	3.7		22,500		N. 1 1011
11	47	М.		34,350	• •	November 7th, cancer of stomach and liver.
				30,600		November 11th.
				105,600!	* 0	November 14th, perforation
40	4.4					peritonitis.
12	41	M.	4,273,000	10,000	57	Stomach, liver, and glands.
13	38	М.	5,432,000	10,190	52	January 6th. Stomach and liver.
				13,653		January 12th.
						January 22d, died.
						·

### CANCER OF THE GULLET.

Most authors are agreed that *no increase*—in fact usually a decrease—of white cells is the rule in this disease. Thus Rieder found 6,900 in one case; Osterspey's two cases showed no leucocytosis, and Escherich and Pée found similar results. This is probably due to the fact that the position of the tumor, by causing starvation, tends to lower the leucocytes, while it belongs to a class of small, slow-growing cancers which do not as a rule tend to produce leucocytosis.

Nevertheless, ten of the eighteen cases in the Massachusetts General Hospital series (see Table LXIII.) did have leucocytosis, perhaps owing to some metastasis or complication. Three others showed a leucocytosis later.

TABLE LXIII.—CANCER OF THE GULLET.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	32			5,400		
2	50			6,400		
3	58	M.	3,488,000	6,800	100	May 11th.
				6,800		May 18th.
4	46	F.		7,000		October 18th.
				10,600		
				5,400		October 19th, before food.
				6,600		October 19th, after food.
				9,860		October 20th.
5	62		4,044,000	7,000	60	December 29th.
				13,750		January 31st.
				14,400		February 25th.
6	67			7,000 a. c.		
				6,900 p. c.		
7	51	M.	2,824,000	7,600	50	Before food.
		3.5		11,500		Four hours later.
8	56	M.	4,920,000	8,725	72	
9	65	Μ.		11,100	68	
10	51			10,300		
11	65	3.5		11,800	00	TT 4 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
12	36	Μ.	0.004.000	11,800	30	Hæmaturia also.
13	49		6,624,000	11,900	90	Vomiting
14	47	3.7		13,700	70	
15	47	M.		15,400	80	
16	38	M.	4 004 000	15,600	60	Desir a dimention
17	67	M.	4,604,000	16,400	60	During digestion.
18	38	F.	4,560,000	20,600	50	

<sup>&</sup>lt;sup>1</sup> Reinbach's two cases showed a diminution in the polymorphonuclear cells, which in all probability means a normal or diminished leucocyte count.

# CANCER OF THE LIVER. (See Table LXIV.)

Out of forty-two cases, leucocytosis was present in twenty-five, others showing a leucocytosis later—a larger proportion than in gastric cancer. The cases were not all primary in the liver or bile ducts, but none originated in the stomach, and in all the greater part of the growth was in the liver itself.

The comparatively great diminution in the red corpuscles will be noted in the Table XLIV. The condition both of red and white cells is doubtless due to the rapid growth of tumors of the liver as compared, e.g., with those of the stomach or lip (see below).

TABLE LXIV.—CANCER OF THE LIVER.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
55	M.	4,170,000	5,000		Bile ducts = starting-point. Autopsy.
61	M.	3,824,000	5,200 6,200	52	Autopsy.
42 52		5,100,000	6.800	80	Bile ducts.
59 44	F.	4,953,000	7,400 7,800	69	January 4th, 1896. Autopsy.
44	r.	3,784,000	19,700	68	February 12th, 1896.
59	M.	4,570,000	8,000	**	Operated.
31 <b>5</b> 9	F.	4,572,000	8,000 8,300	62 63	
46 72			8,500	**	Gall bladder.
72 50	М.	4,100,000	9,000 9,000 a.c.		Bile ducts.
	• •		10,400 p.c.	**	Die dueis.
52			9,100 9,100 a.c.	75	
			8,500 p.c.		
54	М.	4,072,000	9,300	••	Diff., 1,000 cells: poly., 82.4 per cent; small lymph., 8.5; large lymph., 8.1; old lymphocyte, 1.
42		5,600,000	9,600	66	Gall bladder.
35	M.	3,800,000	12,500 9,800		November 3d Poly., 92 per cent; lymph., 8;
			22,000	• •	November 6th \ autopsy.
44	••	3,732,000	9,800	40	December 5th. Poly., 75 per cent; lymph., 22; eosinophiles, 3; reds, pale centres.
			20,000 a.c. 18,800 p.c.		December 21st.
	M.	4,108,000	9,970	45	January 1st, 1896.
67		4.176,000	11,200 10,200	55	January 3d, 1896. Autopsy.
65	m.		10,300	58	
57		3,856,000	10,400 11,400 a.c.	30	Poly., 68 per cent; lymph., 30; eosinophiles, 2.
			16,600 p.c.		
40	::	0.000.000	10,400	60	Operated.
50 64	М.	3,200,000	10,800 11,200	• •	Primary in bile ducts. Autopsy.  April 20th. Bile ducts and gall stones.
01			12,650 a.c.	• •	April 26th.
57	M.		14,750 p.c. 11,150	50	
47	M.		12,200	65	
70			13,000	••	January 20th. Jaundiced.
33			28,400 13,600		January 28th. Died January 30th.
43	M.	4,160,000	14,100	••	July 17th. Autopsy, July 19th.
		0.5			<u> </u>

TABLE LXIV.—CANCER OF THE LIVER (Continued).

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
56	•••	3,956,000	14,200 14,900 a.c. 17,800 p.c.	47	Poly., 84 per cent; lymph., 15.6; eosinophiles, 4. January 17th. Gall stones.
52 64	m.	5,120,000 4,400,000 2,768,000 2,880,000	15,600 15,800 21,900 1,530	65 75 45 45	January 24th.  May 6th.  May 24th.  May 28th.
30	F.	2,928,000 3,660,000	11,700 17,200 16,800	82	June 8th. Poly., 83 per cent; myelocyte, 1.
48	F.	2,900,000	17,500	48	Poly., 92 per cent; lymph., 5.8; eosinophile, 1; myelocytes, 2. Autopsy.
63 31	M.	3,864,000 3,130,000	17,600 18,700 15,600	55 52	December 20th. December 30th. Before food.
37		•••••	14,000 20,600 19,000 a.e. 20,000 p.e.		December 30th. Four hours later.
66 58		3,704,000	21,000 23,200 22,200	50	January 31st. February 12th. Abscess of liver.
Adult. 46	М.	4,408,000 2,824,000	25,500 32,600	70 33	Omental hernia. Purpura hæmorrhagicaInternal hemorrhage. Poly., 84.8 per cent; lymph., 15.2; eosinophiles, 0; no nucleated reds; considerable variation in size; moderate
50	М.	4,544,000 3,136,000 4,056,000	35,600 36,400 23,000 28,000	••	poikilocytosis. November 29th, 1895. December 10th, 1895. January 15th, 1896. February 16th, 1896. Autopsy.

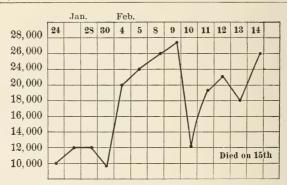


Fig. 35.—Chart of Leucocytes in a Case of Cancer of the Liver.

### CANCER OF THE INTESTINE.

Here the counts range both high and low.

Hayem¹ found cancer of the rectum to show only 9,500 leucocytes. Reinbach² found in three cases of cancer of the rectum mod-

<sup>&</sup>lt;sup>1</sup> Loc. cit.

erate leucocytosis. Only ten of the twenty-five cases in our series (see Table LXV.) showed leucocytosis, and in one of these there was a complicating pylephlebitis which probably raised the count.

The red cells show little change.

TABLE LXV.—CANCER OF THE INTESTINE.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	56	M.	4,408,000	12,700	60	Cancer of duodenal papilla with pylephlebitis.  Autopsy.
2 3 4 5 6 7 8 9	41	F.	5,560,000	5,800	45	Cancer of cæcum. Operated successfully.
3	31	M.	4,921,000	8,800	::	Cancer of hepatic flexure. Operated.
4	33	M.	4,368,000	5,800	83	Cancer of colon. Operated.
5	59	F.	4,800,000	5,500	33	Cancer of cæcum. Autopsy.
6	66	М.	4,268,000	7,150	78	Cancer of intestine (where?).
6	50 58	F.	5.416,000	12,000	50	Cancer of the rectum.
0,	34	M. M.	4,160,000	15,200 15,500	40	Cancer of rectum. Operation.
10	52	M.		7,400	$\frac{40}{55}$	Metastases, primary in sigmoid. Metastases, primary in sigmoid.
11	47	F.		9,300	63	Cancer of cæcum.
11 12 13	28	M.		5,300	72	Cancer of cæcum. Operation.
13	52	M.	2,424,000	7,800		Cancer of cæcum.
10	010	24.	2,440,000	6,800		No digestion leucocytosis.
14	59			6,000	35	December 7th.
			3,452,000		40	December 9th. Polynuclear, 65.6 per cent; lym-
- 1						phocytes, 31; eosinophiles, 3; basophiles, .4.
			3,840,000	11,700	40	December 21st.
15	62			6,400 a.c.		Hepatic flexure.
10			0 504 000	10,000 p.c.	* *	7 // 0 7 7 7 00
16		• •	3,504,000	7,400 a.c.	50	Hepatic flexure. Polynuclear, 80 per cent; lym-
17	39			8,300 p.c. 7,500		phocytes, 19; eosinophile, 1.
18	50	• •		7,800		
19	36	::	3,504,000	9,800	40	Operated.
20	34		4,524,000	10,800	38	Rectal. Polynuclear, 78 per cent.; lymphocytes,
NO	OI.		1,000	20,000	90	19.8; eosinophiles, 2.2.
21	45		3,358,000	11,500	25	Polynuclear, 68 per cent.; lymphocytes, 28.5;
			,555,550	,		eosinophiles, 3.5.
22 23 24	17			13,600		<u></u>
23	53		5,960,000	13,700	60	
24	46			21,600	80	Rectal and omental.
25	62			25,200	75	

# CANCER OF OMENTUM AND ABDOMINAL ORGANS GENERALLY.

The nineteen cases seen at the Massachusetts General Hospital in which cancerous tissue was pretty generally distributed through the abdominal organs, all showed leucocytosis with six exceptions (see Table LXVI., A).

<sup>&</sup>lt;sup>1</sup> Apparently—that is, the percentage of adult cells was increased. He did not count the leucocytes as a whole.

Table LXVI., A. — Cancer of Omentum and Abdominal Organs Generally.

Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
50	F.		Greatly increased.	Markedly diminished.	Primary in pancreas. Differential count of 400 cells: Polynuclear, 84.5 per cent; small lymphocytes, 8; large lymphocytes, 5; eosinophiles, 2.5. Autopsy.
63 47 59		5,440,000 6,072,000	5,350 5,800 6,000	65 35	Colon.
90	• • •	3,452,000		40	December 9th. Polynuclear, 65.6 per cent; lymphocytes, 31; eosinophiles, 3; basophiles, 4.
48	M.	3,840,000	11,700 7,250 6,500 t	40	December 21st. May 13th.
			7,300		May 20th. No digestion leucocytosis.
42	M.	4,560,000	7,800	60	October 13th. Polynuclear, 88 per cent; lymphocytes, 10; eosinophiles, 2.
67			10,600 7,800 a.c. 8,100 p.c.		October 16th.
47			8,000	65	Cæcum.
26	M.		8,300 9,000		General in abdomen.
63		2,860,000	10,600 9,600	35	Polynuclear, 84 per cent; lymphocytes, 10.2; eosinophiles, 6; myelocytes, 8; normoblast = 1.
65	M.		11,700	20	7.1
44	• •		13,600 14,200	68	February 10th. February 18th. Peritoneal. Autopsy.
Adult.	M.	3,772,000	13,700		Autopsy.
28		4.496,000 2,995,000	152,000 18,000	45 60	Peritoneal.
	••	2,990,000	10,000	00	Polynuclear, 79; lymphocytes, 14.5; eosinophiles, 3.5. Kidney and spleen.
46		8,000,000	20,400	50	Polynuclear, 88 per cent; lymphocytes, 10;
			12,600	65	eosinophiles, 2; normoblasts = 16; megalo- blasts = 2. Count 500 cells. Size reds all right.
Adult.	F.	5,500,000	26,200		Autopsy.
45	F.		27,400	3533	Questions of aneurism. Autopsy.
Adult.	М.	******	Greatly increased.	Markedly diminished.	Differential count of 500 cells. Polynuclear, 80 per cent; lymphocytes, 20.

### CANCER OF THE KIDNEY.

Of ten cases which I have examined (see Table LXVI., B) eight showed large leucocy tecounts—viz., 12,900, 19,980, 25,000, 27,000, 28,500, 43,100, 82,000, and 91,000. In three of these cases, however, the tumors may have been sarcomata, as no microscopical examination was made. Most of the cases had fever, chills, and signs of inflammation, which may account for part of the leucocytosis.

TARLE LXVI., B.—CANCER (OR SARCOMA) OF KIDNEY.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1 2 3	58 48		3,840,000	7,600 8,100	50	Autopsy.
3	76	••	5,046,000	9,100	45	Sarcoma.

TABLE LXVI., B.—CANCER (OR SARCOMA) OF KIDNEY (Continued).

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
4	14			19,980 11,600 a.c. 12,900 p.c. 7,900 a.c. 9,000 p.c.	::	Autopsy. March 14th. Polynuclear, 72 per cent.; lymphocytes, 27; eosinophile, 1. March 17th.
5 6	53	m.	4,312,000	23,000 25,000	32	Autopsy. Differential count of 800 cells: Polynuclear, 80.9 per cent.; lymphocytes, 15.8; eosinophiles, 3.3. No nucleated red cells.
7	2	F,	3,756,000	27,000		Differential count of 500 cells: Polynuclear, 66 per cent.; lymphocytes, 29.5; eosinophiles, 2; myelocytes, 2.5; normoblasts, 24; megaloblasts, 2. Autopsy.
8	57	F.	5,200,000	28,500	••	Supposed leukæmia. Differential count of 500 cells: Polynuclear, 81.8 per cent.; small lymphocytes, 12; large lymphocytes, 4.2; eosino-
9	49	F.	3,360,000	43,100	••	philes, 2. Autopsy. Supposed leukemia. Differential count of 1,000 cells: Polynuclear, 92.9 per cent.; lymphocytes, 6.2; myelocytes, 9; normoblasts, 2; megalo-
10	50	F.	4,111,000 2,780,000	82,000 91,000		blast, 1. Autopsy. July 8th. Polynuclear, 98 per cent.; lymphocytes, 2.

Von Limbeck's' case mounted steadily from 18,514 to 80,541.

#### CANCER OF THE UTERUS.

In six cases Hayem<sup>2</sup> found no increase—the counts ranging from 4,575 to 9,500 with an average of 7,800.

Rieder,<sup>3</sup> on the other hand, in a single case found 30,800, and the seven cases counted at the Massachusetts General Hospital showed a leucocytosis in five (see Table LXVII., A).

There is need of more data on this subject.

TABLE LXVII., A.—CANCER OF THE UTERUS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	35			6,400	62	
1 2 3	43		4,772,000	8,600	62 43	·
3	43 59		2,,,,,,,,,,	16,800		First day.
				7,400 a.c.	::	Third day.
			ĺ	12,000 p.c.		
4	48	F.	2,696,030	19,400	20	October 26th.
-	10		3,232,000	30,700	20 27	October 28th.
5	51	F.	0,000,000	34,900		Differential count of 1,000 cells: Poly., 88 per
	01	r.		01,000	••	cent; small lymphocytes, 11.7; eosino- philes, 2; myelocytes, 1. Two normoblasts.
16	21	F.	2,889,680	22,250		phnes, .2, myelocytes, .1. Two normobiasts.
6	31 28	F.		20,170	75	Ureter blocked: anuria nine days. Autopsy.
_	20	E.		20,110	10	oreter blocked, andria fifie days. Addopsy.

<sup>1</sup> Loc. cit.

<sup>&</sup>lt;sup>2</sup> Loc. cit.

<sup>3</sup> Loc. cit.

# TABLE LXVII., B.—CANCER OF THE OVARY.

-									
No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.			
1 2 3	50 36	F. F.	3,532,000 4,500,000 3,248,000	16,400 25,000 32,800	50 62	Operation. Operation.			
	CANCER OF THE PROSTATE.								
1	63		2,596,000	9,200	35	December 13th.			
			2,212,000	11,000	••	December 19th. Polynuclear, 74.4 per cent; lymphocytes, 23.6; eosinophiles, 2.			
2	45 51	M.		10,200 18,000					
				CAN	NCER OF	THE LIP.			
1	51	M.	7,000,000	6,300	1				
				CANCI	ER OF T	HE BREAST.			
1 2	31	F.	6,000,000	8,200 Not		Differential count of 600 cells: Poly., 72.4 per			
			• • • • • • •	increased.	• •	per cent; lymphocytes, 25.4; eosinophiles, 2.2.			
3	3	F.		Marked increase.	**	Differential count of 400 cells: Poly., 89 per cent; lymphocytes, 11.			
5	57 60	• •	5,200,000	12,200 18,000	68	First day.			
	1	1		14,000	• •	Third day.			
				CAN	CER OF	THE NECK.			
1	42	М.	******	Marked increase.	••	Poly., 88.5 per cent.			
				CANCEL	R OF THE	E PANCREAS.			
1 2	55 56	M. M.		18,300 17,600	70	Metastases. Liver and spleen also.			
3	64	М.		15,900	••	General peritonitis.			
				CANC	ER OF V	Vertebræ.			
1	62	F.	1	13,200					
			Aı	DENOMA OI	THE S	UPRARENAL BODY.			
1	59	M.		24,200		Autopsy.			
					MEDIAST	INUM.			
	25	····		10,700	70	April 20th. Polynuclear, 87 per cent.			
				9,300 8,300		April 27th. Lymphocytes, 12 "April 27th. Eosinophiles, 1"			
	47		5,008,000	6,800 12,800	30	May 1st. July 7th. Stricture eesophagus. Larynx.			
	ŀ	1		14,000		July 18th. No autopsy.			
					Skui				
	57 70			9,200 8,600	• •	Cerebral. May 7th.			
				15,800 14,600	• •	May 22d. May 28th. Metastases.			
					GENEI	RAL.			
	63		4,700,000	14,600	70 60	Multiple myelome (Wwight)			
	•••		4,700,000	5,000	00	Multiple myeloma. (Wright.)			

Cancer of the lip has apparently been neglected so far as blood examination is concerned. Hayem, Rieder, and Reinbach give but one case each, the counts being respectively 7,000, 11,600, and "not increased." In a single case at the Massachusetts General Hospital I found 6,300.

The following scattered counts may be added: Cancer of tongue, 7,000 (Hayem); cancer of scrotum, 6,700 (Hayem); cancer of navel, 7,100 (Hayem); cancer of larynx, 7,200 (Hayem), 16,000 (Reinbach); cancer of ovary, 25,000 (Massachusetts General Hospital) and "no increase" (Reinbach); cancer of neck, 20,000, Massachusetts General Hospital, and no increase (Reinbach); cancer of pancreas: Hayem, 2 cases—9,400 and 9,900; Schneider, 1 case—12,000; cancer of vagina, 9,800 (Rieder); cancer of penis, 7,000 (Hayem); cancer of thyroid, 70,000 (Hayem) (a very rapidly growing tumor); cancer of mediastinum, "marked increase" (Reinbach); cancer of prostate, 10,200.

## Qualitative Changes in the Leucocytes.

1. The percentage of polymorphonuclear neutrophiles is usually high in cases with leucocytosis and normal in those without it. rule holds for perhaps three-fourths of the cases, but there are many exceptions to it. For instance, Taylor<sup>2</sup> reports 27,840 leucocytes with 65.6 per cent polymorphonuclear cells, 14,800 leucocytes with 66.2 per cent polymorphonuclear cells, 25,000 leucocytes with 58.2 per cent polymorphonuclear cells, 45,000 leucocytes with 43.7 per cent polymorphonuclear cells, the last a marked lymphocytosis. On the other hand, he found 88.7 per cent of polymorphonuclear cells in a total leucocyte count of 3,000. My own experience is similar—i.e., 88 per cent of polymorphonuclear cells with a total count of 7,800 leucocytes, though I have never seen so marked a lymphocytosis as was present in Taylor's cases. He also noted a relative increase in the large lymphocytes which my counts have not shown. Osler and McCrae found an average of 81 per cent of polymorphonuclear cells in 22 cases, the higher percentages being in the cases with highest total leucocyte count. These writers confirm the

<sup>&</sup>lt;sup>1</sup> Braun (Wien. med. Woch., 1896, p. 582) mentions a cancer of the prostate in which the leucocytosis, instead of being made up mostly by the adult leucocytes, was associated with a large increase of the small lymphocytes together with numerous eosinophilic myelocytes.

<sup>&</sup>lt;sup>2</sup> Taylor: Internat. Med. Mag., July, 1897.

observation of Taylor that the large mononuclear and transitional leucocytes are often relatively increased in cancerous disease. Taylor found in 15 cases with leucocytosis an average of 19.3 per cent of these cells and in 6 cases without leucocytosis 26 per cent. Eight of these cases were cancer of the stomach—the remainder cancer of other organs. All were cachectic. Osler and McCrae in 22 cases of gastric cancer record an average of 8.5 per cent of large mononuclear and transitional varieties. They do not agree with Taylor in believing the excess of these cells is sufficient to be of diagnostic value.

Reinbach found in 8 cases with leucocytosis 89 per cent in 2 cases and 87, 86, 83, 81, 80, and 77 per cent in others. In the Massachusetts General Hospital series the following percentages occurred: When no leucocytosis was present, 88.7, 88, 86, 79, 66, 62.5, 62, 60, 57 per cent, etc. With leucocytosis, 96, 98, 92, 90, 90, 88, 87, 86, 84, 83, 74 per cent, etc. (see Tables LXII., LXIV., LXVII.).

- 2. Eosinophiles are not always notably decreased (as they are in many other leucocytoses) nor are they increased except when bone metastasis occurs (see below). In Reinbach's 16 cases the average percentage was 2 + per cent. In Osler's 22 cases it was 1.1 per cent. In the Massachusetts General Hospital cases the average was 1.2 per cent, but in 7 of the 38 cases in which differential counts were made, no eosinophiles were seen.
- 3. Myelocytes.—Perhaps more commonly than in other conditions except leukæmia and pernicious anæmia, we find in malignant disease small percentages of myelocytes, as the following cases show:

Case I.—Extensive abdominal cancer; great cachexia. Six hundred cells showed:

	Per cent.
Polynuclear neutrophiles	. 89.4
Lymphocytes	. 10.
Eosinophiles	1
Myelocytes (3 in 600 cells)	5

CASE II.—Cancer of uterus; marked cachexia and leucocytosis One thousand cells showed:

	Per cent.
Polynuclear neutrophiles	. 82.3
Lymphocytes	. 17.3
Myelocytes (4 in 1,000 cells)	4

CASE III.—Cancer of uterus; died two days later. Red cor-

puscles, 7,000,000; white, 62,000. Considerable stasis helps to explain the count. Differential count of 500 cells showed:

	Per cent.
Polynuclear neutrophiles	. 93
Lymphocytes	
Eosinophiles	0
Myelocytes (5 out of 500)	. 1

CASE IV.—Cancer of liver, jaundice, and cachexia; died soon after. Differential count of 500 cells showed:

	Per cent.
Polynuclear neutrophiles	. 92.
Lymphocytes	. 6.
Small myelocytes	. 1.2
Large myelocytes (4 in 500)	

Case V.—Cancer of abdomen; cachectic. Differential count of 1,000 cells showed:

Polynuclear neutrophiles	r cent. 82.
Lymphocytes	
Eosinophiles	1.
Myelocytes (4 in 1,000)	.4

CASE VI.—Cancer of stomach, liver, etc., with perforated stomach; cachexia. Leucocytes, 105,000. Fifteen hundred cells showed:

	Per cent.
Polynuclear neutrophiles	. 90.7
Lymphocytes	. 4.8
Eosinophiles	2
Myelocytes (68 in 1,500)	. 4.3

Case VII.—Cancer of uterus; cachexia. In 1,000 cells there were:

	Per	r cent.
Polynuclear neutrophiles		88.
Lymphocytes		11.7
Eosinophiles		2
Myelocytes		.1

Case VIII.—Cancer of kidney; great cachexia. In 1,000 cells there were:

	er cent.
Polynuclear neutrophiles	92.9
Lymphocytes	6.2
Myelocytes	.9

Case IX.—Cancer of kidney; great cachexia. Leucocytes, 27,-000. Five hundred cells showed:

	]	Per cent.
Polynuclear neutrophiles		66.
Lymphocytes		29.5
Eosinophiles		2.
Myelocytes		2.5

# Case X.—Cancer of liver. Five hundred cells showed:

	P	er cent.
Polynuclear neutrophiles		92.
Lymphocytes		5.8
Eosinophiles		.2
Myelocytes		

About one-half of all the cases of cancer examined by me have shown myelocytes.

Epstein<sup>1</sup> in a case of cancer with metastatic bone nodules noticed large numbers of nucleated corpuscles (normoblasts and megaloblasts) and myelocytes, but I think the association was a mere coincidence, since I find that myelocytes and erythroblasts are very commonly present in cachexia from any cause.

### SARCOMA.

In general the effects of sarcoma are like those of cancer, but worse. Great anæmia and higher leucocyte counts are the rule. The literature of the subject is rather scanty.

Red Cells.—Hayem in a case of osteosarcoma counted the red cells at 663,400 per cubic millimetre.

Laker<sup>2</sup> describes an "abdominal cystosarcoma" in which two counts of red cells showed 2,800,000 and 2,500,000.

Von Limbeck <sup>3</sup> in 1 case found 1,118,000, and in another 2,240,-000. Both were osteosarcomata.

Sadler<sup>4</sup> in 3 cases found 2,710,000, 3,637,000, 4,500,000.

Rieder<sup>8</sup> in 3 cases (all osteosarcomata) found 1,846,160, 3,700,-000, and 3,995,000.

The Massachusetts General Hospital blood counts include 19 cases in which the red cells were counted (see Table LXVIII., A and B), the average being 4,400,000, not nearly so low as that recorded

<sup>&</sup>lt;sup>1</sup> Wiener med. Presse, December, 1894.

<sup>&</sup>lt;sup>2</sup> Wien. med. Woch., 1886, p. 926.

<sup>&</sup>lt;sup>3</sup> Loc. cit., p. 343.

<sup>&</sup>lt;sup>4</sup> Loc. cit., pp. 38, 39.

<sup>&</sup>lt;sup>5</sup> Loc. cit., pp. 98, 100.

by other observers; still low counts occurred (2,706,000, 2,637,000, 3,842,000).

The qualitative changes in the red cells consist (as in cancer) of the "degenerative" changes (deformities in size and shape, englobular changes) present in marked cases, and the presence of nucleated corpuscles, when cachexia is marked.

TABLE LXVIII., A.—SARCOMA WITH LEUCOCYTOSIS.

No.	Age.	Sex.	Red cells.	White ceils.	Per cent hæmo- globin.	Remarks.
ON   123			4,188,000 4,312,000 4,000,000	98,000 25,000 44,600	32 42	Polynuclear cells, 90.2 per cent. Polynuclear cells, 80.9 per cent. Polynuclear cells, 70 per cent (infant of twenty months).
5	21 35	F. F.	2,706,000 4,560,000	56,000 17,000 23,900	65	Sarcoma of kidney. Autopsy.  Melanotic sarcoma of all abdominal organs (bone metastasis?). November 30th, 1895. Differential count of 600 cells: Polynuclear, 71 per cent; small lymphocytes, 11; large lymphocytes, 5.2; eosinophiles, 12.4 (!); myelocytes, 4.  December 7th.
				33,400 37,900 41,200 33,000 36,000		December 18th. December 19th.  December 22d. December 26th.
- 1				40,200		January 14th.
				55,400		January 28th.
6	46	M.	4,700,000	16,000		Sarcoma of abdominal organs.
7	32	M.	2,630,000	19,000 24,000		Three days later. Autopsy. General sarcomatosis.
•	020	zu.	2,900,000	21,000		One week later. Autopsy.
8	24	M.	4,352,000	13,600		Sarcoma of kidney.
9	41	M.	3,842,000	61,100	55	Sarcoma of lung, etc. Autopsy.
10	68	F.	6,200,000	16,000		Sarcomatosis.
11	48	М.		in- crease.		Differential count of 700 cells: Poly., 70 per cent; lymphocytes, 22; eosinophiles, 1; myelocytes, 7. Sarcomatosis.
12	57	М.	4,180,000	13,000 $16,250$ $15,180$	47	Melanotic sarcoma of abdominal organs. One week later.
13	Adult.	M.		18,000		Sarcoma of abdominal organs.
14				Great in-		Osteosarcoma (thigh). Differential count of 500 cells: Poly., 74 per cent; small lymphocytes, 19;
15				Great in-		large lymphocytes, 6; eosinophiles, 1. Sarcoma of abdominal organs. Differential count of 800 cells: Poly., 84 per cent; lymphocytes,
16				crease.		15.5; eosinophiles, 5. Sarcoma of abdominal wall.
17	36	М.		13,200 6,700		barcoma of aodominar wall.
18	30		4.512,000	26,100	70	Neck.
			5,422,000	28,500	75	One month later. Polynuclear, 89 per cent; lym-
10	F0			10.000		phocytes, 9.8; eosinophiles, 1.2.
19 20	58 58			19,980 14,100		Neck. Autopsy. Cæcum.
21	10			10,200	70	Abdominal wall.
22	45		5,480,000	18,400	35	December 2d. Adrenal.
	10		0,100,000	21,600		December 5th.
				16,600	40	December 16th.
- !						

Small tumors are often without any effect on the blood (see Table LXVIII., B). According to v. Limbeck ' this is oftener true than in cancer.

<sup>&</sup>lt;sup>1</sup> Loc. cit.

TABLE LXVIII., B.—SARCOMA WITHOUT LEUCOCYTOSIS.

No.	Age.	Sex.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1 2 3 4 5 6 7 8 9	29 37 ? 24 46 44 58 47 54 35	M. F. M. M	5,280,000 4,980,000 4,946,000 4,9452,000 5,390,000 4,288,000	8,200 9,000 9,000 6,000 6,100 7,600 6,500 5,600 9,800 5,100 5,700 a.c. 8,600 p.c.	55 70 65 72 65	Sarcoma of testicle. Sarcoma of ovary. Osteosarcoma of shoulder. Small recurrent sarcoma of groin. Glands. Ovary. Cutaneous. Kidney operated. Kidney operated. Retroperitoneal. Polynuclear, 66 per cent; lymphocytes, 33.4; eosinophiles, .6. Reds good.

Hæmoglobin.—Reinbach's 20 cases ranged between 23 and 75 per cent, averaging 52 per cent.

Bierfreund <sup>2</sup> in 29 cases found variations between 40 and 75 per cent.

Von Limbeck's 2 cases had 28 and 48 per cent respectively.

Rieder's 4 cases showed at the beginning of treatment 29, 56, 57, and 65 per cent respectively, but in 1 case the hæmoglobin went down gradually while under observation until it reached 6 per cent (!), the lowest point, Rieder says, that he has ever seen in any disease.

Sadler's cases showed 33, 45, and 78 per cent.

In the 16 cases of Table LXVIII. in which this point was noted, the average is 59 per cent.

On the whole, the coloring matter seems to be more diminished than in most cases of cancer.

Leucocytes.—The following tables, slightly modified from v. Limbeck, show the important points.

No.	Observer.	Diagnosis.	Count.
1 2 8 4	Hayem. Alexander. "	Osteosarcoma. " " " "	11.250 52,700 16,430 16,275 17.050
5	.c .c	cc cc	15,900 15,570 13,020

<sup>&</sup>lt;sup>1</sup> Loc. cit.

No.	Observer.	Diagnosis.	Count.
7. 8. 9. 10. 11. 12. 13. 14. 15. 16.	Alexander.  "Rieder.  " v. Limbeck.  Reinbach.  Mass. General Hospital.	Osteosarcoma.  ""  ""  ""  ""  ""  ""  ""  ""  ""	10,950 12,090 11,248 12,700 10,900 9,100 8,000 26,800 20,000 13,000 21,000 9,000
		Average,	17,000 ±

No.	Observer.	Diagnosis,	Count.
1	Hayem. Alexander.  " " v. Limbeck.  " Sadler. "	Lymphosarcoma.  " " " " " " " " " " " " " " " " " "	11,700 19,910 19,530 11,696 11,470 10,540 55,100 38,000 10,800 33,248 19,299 9,044
		Average,	20,000 +

	anosarcoma, 41,600
2	" 28,500 " 22,300 " 25,000 " 8,000 " 37,900 " 13,000 Average, 25,100 +

For other sarcomata, see Table LXVIII., A and B.

On the whole, leucocytosis appears to be more constant and of greater extent in sarcoma than in cancer.

### Qualitative Changes.

1. The increase of polymorphonuclear leucocytes which we find in most forms of leucocytosis is not always present in sarcoma<sup>1</sup> and seems to be less frequent than in cancer (see Cases 5, 11, 14, Table LXVIII.).

As in cancer, it may be present when no increase in the total leucocytes is to be found, and may be the only indication of any disease in the organism.

2. A few cases are on record in which a large percentage of eosinophiles has been present.

Reinbach found 48 per cent of eosinophiles in a case of sarcoma of the neck with sloughing and ulcerative endocarditis, the percentage continuing over 40 for several weeks.<sup>2</sup> Autopsy showed sarcomatous nodules in the bone marrow. In another case, a tumor of the abdomen, the eosinophiles were 10.5 per cent, and in two others 8 per cent.

A case of apparent sarcoma of the abdominal organs (no autopsy) at the Massachusetts General Hospital in January, 1896, had 12.4 per cent of eosinophiles.

Such cases should certainly make us think of bone metastases, and Neusser speaks of osteosarcomata as being accompanied by eosinophilia, but the evidence is as yet fragmentary.

<sup>1</sup> Palma (Deut. med. Woch., 1892) reports lymphocytosis in sarcoma.

<sup>2</sup> The full counts are as follows:

April 4th, 1892.	May 20th, 1892.
Red cells.       5,396,000         White cells.       120,000 (!)         Hæmoglobin.       60 per cent.	Red cells.       4,512,000         White cells.       52,000         Hæmoglobin       55 per cent.

#### DIFFERENTIAL COUNTS.

	April 4th.	May 1st.	May 20th.	May 26th.
Poly. neut Eosinophiles Lymphocytes Myelocytes	Per cent. 48 48 2.7 1	Per cent. 51 46 2.32 .68	Per cent. 55 + 42 1.5 .64	Per cent. 51 + 44 + 3.2 .8

3. Myelocytes.—Reinbach's case just described had a low percentage of myelocytes.

The following cases illustrate the same point:

Case I. is a case of sarcomatosis in a man in whom sarcomatous nodules were distributed all over the internal organs and in the skin. A differential count of 700 white cells showed in his case:

	Per	cent.
Typical myelocytes (over $15\mu$ )		2
Small myelocytes (under $15\mu$ )		5
Lymphocytes		22
Polynuclear neutrophiles		70
Eosinophiles		1

The autopsy showed no special lesions in the spleen, glands, or bone marrow, except those due to the sarcomatous nodules.

Case II.—Sarcoma of the abdominal wall. A differential count of 800 cells showed:

	Per cent.
Polynuclear neutrophiles	. 84.
Lymphocytes	. 10.5
Large lymphocytes	5.
Eosinophiles	2
Myelocytes	3

CASE III. (No. 5, Table XLVIII., A).—Six hundred cells contained:

	Per cent.
Polynuclear neutrophiles	. 71.
Lymphocytes	. 16.2
Eosinophiles	. 12.4
Myelocytes	4

Summary of Blood Changes in Malignant Disease.

- 1. Small, slow-growing tumors and the early stages of all tumors may have no effect on the blood appreciable by our present methods of examination.
- 2. In advanced cases the red corpuscles often become thin, light, and pale, and finally their number may be greatly decreased, the counts running sometimes as low as in pernicious anæmia. In this respect, as in others, sarcomata seem to injure the blood more than cancers.
- 3. The color index is always below 1, but is rarely as low as we find it in severe chlorosis.

- 4. Normoblasts and megaloblasts (the latter being in the minority) may occur, the former even in the absence of severe anæmia. Deformities in size and shape are common.
- 5. Leucocytosis is present in the cachectic end-stages of many cases, but is frequently absent in small tumors of slow growth and without metastases. The polymorphonuclear cells are often relatively increased.
  - 6. Fibrin is not increased.

### Diagnostic Value.

- 1. When we are dealing with an obscure, deep-seated disease, if hemorrhage is excluded, the presence of persistent leucocytosis suggests suppuration or malignant disease (rather than tuberculosis or syphilis, for example), and excludes any simply functional or hysterical affection. The absence of leucocytosis, however, does not exclude malignant disease, though it makes suppuration very unlikely.
- 2. Between malignant disease and suppuration—if the other signs and symptoms do not decide—there may be nothing in the blood to decide. In decided pyæmia we may get pyogenic cocci from the blood by culture, but a negative result would not exclude the suppurating focus.

The absence of any increase of fibrin in the blood speaks against suppuration, and therefore in favor of malignant disease; but the presence of increased fibrin network is not decisive either way, as it may be met with in connection with neoplasms, though more common in suppuration.

- 3. Between malignant disease and hemorrhage a marked anæmia favors the latter, provided the case is a recent one; for the anæmia of malignant disease is comparatively slow to develop. The leucocytes give no help.
- 4. Between cancer and ulcer of the stomach, if there has been no recent hemorrhage, leucocytosis favors cancer; but its *absence* is of no weight either way.

The hæmoglobin is said to decrease steadily in cancer, while in ulcer it tends to return toward normal after the cessation of hemorrhage.

The presence and persistence of digestion leucocytosis speak against cancer, and its absence in favor of cancer. It must be remembered, however, that any variety of catarrh or dilatation

(should such be present) can also prevent digestion leucocytosis, and that the latter is not invariably present even in health.

- 5. Between cancer of the liver or bile ducts on the one hand and simple gall-stone colic or gall-stone obstruction, the presence of leucocytosis favors cancer. As usual, however, its absence does not exclude cancer, and we must bear in mind that gall stones with cholangitis may raise the leucocyte count as much as cancer. Simple cysts or echinococcus cysts cause no leucocytosis, nor does syphilis of the liver.
- 6. The appearance in the blood of large numbers of eosinophiles, myelocytes, and nucleated corpuscles during the course of a malignant disease points to a bone metastasis.
- 7. When a leucocytosis which has disappeared after removal of a neoplasm reappears, we may expect recurrence of the growth shortly.
- 8. A steadily increasing leucocytosis in a case of malignant disease points to a rapidly growing tumor or to the occurrence of metastasis.
- 9. Between malignant disease and pernicious anæmia, the diagnosis rests on the following points:
- I. Color index low in malignant, apt to be high in pernicious anæmia.
- II. Leucocytes often increased in malignant, diminished in pernicious anæmia.
- III. Lymphocytes often decreased in malignant, increased in pernicious anæmia.
- IV. Average size of red cells often decreased in malignant, and often increased in pernicious anæmia.
- V. If nucleated red corpuscles are present the normoblasts are in a majority in malignant disease, and in a minority in pernicious anæmia.
- 10. The presence of leucocytosis is against the benignness of any tumor.
- 11. When no actual increase of leucocytes is present, an increased percentage of the polymorphonuclear variety among those present may have the same significance as a leucocytosis.

### CHAPTER XI.

### BLOOD PARASITES.

Examination for the Plasmodium Malariæ and its Products.

I. Time for Examination.—It is often stated that the organism is most easily found during the chill. But this is not the writer's experience. During a chill it is often difficult and sometimes impossible to find the organisms. Eight hours before or after a chill is the most favorable time (Thayer), although parasites have been found as late as forty-eight hours after the last chill. During the chill many organisms retire to the internal organs.

The number of organisms varies a great deal. In some cases they are present in every field of a one-twelfth immersion lens, while in others we may find only one after an hour or more of patient search. In some cases of coma Ewing had to search one and two hours before finding a single parasite. In the majority of the cases occurring near Boston, it needs but a few minutes' search to find them if the blood be taken within twelve hours before or after a chill, and provided no quinine has been lately given. Occasionally in mild cases the organisms are very scanty; and it may be almost impossible to find any. Theobald Smith agrees with Ewing that when the parasites are scarce, especially when they are of the small unpigmented form, a prolonged search through fresh blood has frequently proved negative, although a few minutes sufficed for the discovery of one or more minute parasites in the stained specimen. The quartan and æstivo-autumnal forms of malaria are so rare in New England that I shall not attempt to describe in detail the parasites found in them, but shall confine myself mostly to the parasites of common tertian and double tertian fevers with which I am personally familiar.

II. Method of Examination.—A slide of fresh blood is prepared as above described (pages 6-8) and examined with a one-twelfth immersion lens. Lower powers should not be used, although in

<sup>1</sup> In cold weather both slide and cover should be warmed before using. Indeed this is always well, as it makes the corpuscles spread better.

skilful hands they are often sufficient. Portions of the slide in which the corpuscles do not overlie each other should be chosen for examination. As we pass the slide along beneath the lens it is well to be on the lookout for any specially large or specially pale corpuscle. Such a one will catch the eye if we are on the watch for it, even though the slide is being passed along very rapidly, and all such should be carefully examined.

Another thing to watch for is anything black or dark brown. If the slide is not perfectly clean, or if the cover-glass has touched the skin in collecting the blood, there will often be black spots which make us pull up short and examine, only to find that they are bits of dirt. This loses time, and hence, as above noted, the importance of care and cleanliness in the earlier stages of the process.

Besides any strikingly pale or swollen corpuscle or any black dots, we should be on the lookout for any movements in the field. The movements of Müller's "blood-dust" (see page 60) are often mistaken by beginners for those of the malarial organism. Their greatly smaller size and extra corpuscular position serve to distinguish them in most cases. I have sometimes thought I saw pigment in these bodies. If, as Stokes believes, the "blood-dust" is derived from the leucocytes, it is possible that they might carry out with them some pigment ingested by the leucocyte.

Flagellate bodies may be studied in fresh specimens, if possible, on a warm stage. Usually they appear only after the lapse of ten to twenty minutes from the larger tertian or crescentic æstivo-autumnal organisms. The addition of a little water or salt solution may facilitate the escape of the parasite from the red cell and the formation of flagella.

Ewing finds that the moist chamber may be secured in a Petri dish with tightly fitting vaselined cover. Wet blotting-paper placed in the dish furnishes the necessary moisture. Specimens spread on slides or covers may be kept moist for ten to twenty minutes in such dishes, and flagellation proceeds with moderate rapidity.

A simple method is as follows: Cut an opening one-half by one inch in a piece of thick blotting-paper and moisten the paper in hot water. Spread two glass slides rather thickly with fresh blood, lay the blotting-paper on one slide, cover the cut opening by the other, specimen side down, and slip a rubber band about both. After fifteen or twenty minutes the slides and paper may be separated and the two specimens dried.

III. The Malarial Organism.—(a) It practically is never to be seen outside the corpuscle. Most malarial organisms are to be found within the corpuscle, and only there.

For those who have not examined many specimens of malarial blood it is a very difficult thing to find the organism at this stage of its growth, and the number of mistakes in diagnosis is very large. I always look with great suspicion on any report of malarial blood as containing *only* "hyaline forms."

In the later stages, when the organism has become well pigmented, there is nothing that at all resembles it, and those who have seen and watched it a few times can hardly mistake anything else for it. Not so with the so-called "hyaline" or youngest form of the organism. Personally I think the name "hyaline bodies" is responsible for a part of the mistakes. We are led to expect something more shiny and refractile than the organism really is, and so are misled by the brilliant white circles to be found at the centre of many normal corpuscles under certain conditions of light and partial drying up. Time and again I have been asked to look at malarial organisms (always the "hyaline" forms), and found nothing more than one of these effects of light which can be found in any normal blood, if the conditions are right. There are certain marks by which we can exclude these artifacts from consideration:

- I. They are generally far too numerous to be malarial organisms. One usually finds a dozen or more in a field which would be almost unheard of with the plasmodium malariæ.
- II. They are generally in the centre of the corpuscle, while the young malarial organism is almost never at the centre.
- III. They are almost invariably round, the malarial organism being generally more irregular and branching.
- IV. They seem to increase and diminish in size as we focus up and down upon them, while the malarial organism only grows dimmer or clearer.
- V. They are, as before mentioned, more brilliantly white and shiny than the malarial organism, which has often a faint tinge of yellow, although much paler than the surrounding corpuscle substance.
- VI. Their edges are sharper, the malarial organism often fading off very gradually into the corpuscle color.
- <sup>1</sup> Except degenerate forms, free flagellæ, and spores at the moment of segmentation (*rarely* to be seen). Crescents and ovoid bodies are intercellular.

(AFTER WRIGHT & BROWN.)

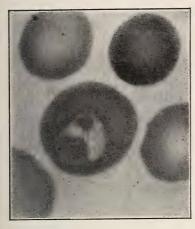


Fig. 1.—Young Non-Pigmented, Hyaline Form of the Æstivo-Autumnal Parasite in a Red Blood Corpuscle.

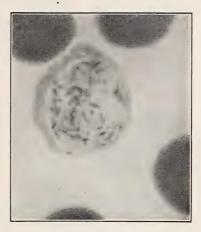


Fig. 2.—Adult Tertian Parasite.

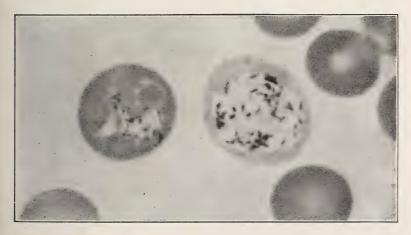


FIG. 3.—An Adult Tertian Parasite, with Rod-Shaped Pigment, in a Red Blood Corpuscle in the Right of the Figure, and in a Corpuscle in the Left of the Figure a Young Pigmented Tertian Parasite and a Signet-Ring Form of the Æstivo-Autumnal Parasite. Thus there is an infection with two kinds of parasites.



- VII. (a) Their movement is different. The malarial organism is not at all the only thing to be seen moving in the blood, as has sometimes been stated. The red corpuscles have the Brownian motion, and as they begin to crenate often move very actively. But their motion is very different from that of the hyaline malarial organism, for the latter changes both its shape and its position in the corpuscle quite rapidly, while the motion of the light space in an ordinary red cell is a wavy undulation of the outlines back and forth without any considerable change of shape.
- (b) As soon as the organism gets any pigment (and there are very few times in the cycle of a malarial case when there are not some pigmented organisms present), the active rapid motion of the black pigment dots is unlike anything else seen in the blood, and when once recognized can never be forgotten or mistaken. It is only when the pigment has ceased moving (owing to the death of the organism) that the differentiation between dirt and malarial pigment becomes difficult.

Sometimes it is really difficult to distinguish motionless pigment in a malarial organism from dirt even on careful scrutiny. The best way is to get a fresh slide when the pigment is in motion.

To any one fairly familiar with the appearance of pigmented forms of malarial organisms, failure to find them in a case of malaria is due generally (1) to too thickly spread a layer of blood, the corpuscles overlying each other; (2) to not looking long enough; (3) to lack of proper light.

(c) The next stage, that of segmentation, is less commonly seen than are those just mentioned, and is only to be satisfactorily observed by using a warm stage (vide supra, page 8) and spending considerable time on the watch for it. Around the central pigment mass we may sometimes see in ordinary specimens (without warm stage) the faint outlines of a group of small spherical, colorless bodies (vide Fig. 2, 9, Plate I.) which are the new generation of young organisms.

Now we should expect that with the next step in the process we should find these young plasmodia free in the plasma or entering a fresh set of red corpuscles. But in the peripheral circulation this is rarely if ever observed. Thayer in his immense experience has never seen them. The next evidence we have of the organism is as a "hyaline" body inside the corpuscle again.

Almost all stages of the growth of the plasmodium which we

can watch in the blood drawn from the peripheral circulation take place within the corpuscle. It is true that as the pigmented organism gets toward its full growth, and before the granules have begun to gather at the centre, we may find it very difficult to find any trace of corpuscle substance around the margin of the plasmodium. Sometimes we see a ring of non-pigmented glistening white substance outside the moving black dots (see Fig. 2, 7, Plate I.) standing out light against the darker plasma. This I suppose to be the remains of the corpuscle. It is not described or pictured in the standard works on the subject.

Occasionally we do find pigmented bodies wholly outside the corpuscle, either partly or fully grown. In the intracorpuscular forms the distinction between plasmodium and corpuscle substance is not, I think, so sharp and clear as one would be led to expect



Fig. 36.—Flagellate Malarial Organisms. (After Thayer.)

from the plates in standard works. With average eyes and lenses the outline of the organism, as distinguished both from its pigment granules and the surrounding corpuscles, is not easy to see. It is the moving pigment granules that attract our notice.

The youngest form of the tertian parasite seen in the red cell is identical in appearance with the spore of the parent rosette. It is a compact spheroidal, or slightly oval, or irregular body, about 2  $\mu$  in diameter. It shows an outer rim of basophilic protoplasm inclosing a single large nuclear body, which is achromic to methylene blue, but stains readily in hæmatoxylon or by Nocht's method, and which is usually inclosed or accompanied by a clear achromatic substance, termed by Gautier "the milky zone."

In the fresh condition these bodies are noticeably refractive, especially the nucleus, change their position but rarely their shape, and are never pigmented.

The young tertian ring: Within a few hours after the chill the parasite is usually found to have assumed a somewhat characteristic



Fig. 4.

Figs. 2 and 4.—Adult Form of Tertian Parasite in a Degenerated Red Blood Corpuscle.

The pigment is seen in the form of rods.



Fig. 5. - Two Tertian Parasites in One Red Blood Corpuscle.



FIG. 6.—An Adult Tertian Parasite with Central Vacuole and Rod-Shaped Pigment in a Distorted Red Blood Corpuscle at the Left of the Figure. At the right of the figure an adult parasite with its pigment gathered together in clumps. This is a tertian parasite in early stage of segmentation. The dark spots at the periphery of the parasite represent the remains of the red blood corpuscle which it has invaded.



ring shape. These bodies measure from 3–4  $\mu$  in diameter, and there is not much increase in bulk for six or eight hours. The tertian ring is rarely as geometrical or delicate as the æstivo-autumnal signet ring. The nuclear body of the tertian ring is its most characteristic feature, appearing as a rather large, achromatic, highly refractive body, after methylene blue, but staining intensely with hæmatoxylon and by Nocht's method.

# Comparison of the Tertian and Æstivo-autumnal Rings.

- (1) According to Ewing, the nuclear body and the chromatin mass of the young tertian parasite are achromatic to methylene blue, which densely stains the nucleus of the æstivo-autumnal organism.
- (2) The shape and contour of the tertian ring is usually coarse and irregular, but the æstivo-autumnal ring is geometrically circular, more delicate, with extremely fine bow, and usually with a typical signet-like swelling.
- (3) One or two grains of pigment are almost invariably found in the early tertian ring, but are with nearly equal constancy absent from the æstivo-autumnal signet ring.
- (4) The tertian ring is usually pigmented before the chromatin becomes subdivided, while the chromatin of the æstivo-autumnal ring is always subdivided before the appearance of pigment.
- (5) The infected cell is usually swollen from the moment of infection by the tertian spore, and commonly shrunken when harboring the æstivo-autumnal ring.

Large tertian rings: After a period of six to eight hours the ring is usually found to have developed an outgrowth which is actively amœboid in the fresh condition and appears in stained specimens as a tongue-like protrusion or turban-shaped mass attached to one segment of the ring. The nuclear body meanwhile increases slightly in size, projecting into the ring, and the chromatin divides into several large granules.

At this period occurs the greatest amœboid activity of the parasite, and in some severe infections the organism may be found fixed in the height of its amœboid excursions. There the ring persists, but the body of the parasite is strung out into a number of slender threads with nodal thickenings.

Tertian spheroidal bodies: During the second quarter of the cycle, the body and nucleus of the parasite develop rapidly in size, amæboid motion and figures gradually diminish, and pigment is

abundantly deposited in the form of dark brown or yellowish grains, showing in the fresh state active vibratory motion. The cell increases in size and its hæmoglobin diminishes. Toward the end of twenty-four hours or possibly somewhat later, the parasite occupies three-fourths of the swollen cell, in the form of a spheroidal or elliptical, homogeneous body, the outer portion of which contains most of the pigment.

Full-grown tertian parasite: The third quarter is occupied by the continued growth of the parasite in the form of a large homogeneous, richly pigmented body, which finally occupies at least fourfifths of the swollen cell.

Pre-segmenting bodies usually begin to appear in the blood eight to ten hours before the chill. The pigment is gathered in a reduced number of coarse grains or spindles which lie in the body of the parasite, in a position determined by that of the new multiple nuclei.

Tertian rosettes are usually seen in the circulation three or four hours before the chill, most abundantly just before the chill, rapidly disappearing after the chill.

The earliest form of the æstivo-autumnal parasite is often distinguished from the tertian by the shrinkage of the cell, low refractive index, and it is never pigmented.

The astivo-autumnal signet ring is a very characteristic shape assumed by the parasite at a very early period. It is noted that in some cases the rings fail to exhibit this thickening but remain of a uniform but very fine calibre throughout. Multiple infection with the young rings is very common; three parasites are often found in the same red cell, and occasionally four. The signet-ring forms frequently reach a diameter of  $4~\mu$ ; beyond this size, when persisting in the finger blood, the growth of the parasite produces an irregular body in which the outline of the ring becomes more or less obscure. The full development of the large signet rings appears to require about twenty-four hours. In the majority of cases the ring forms seen in the peripheral blood fail to show any trace of pigment.

The later forms of the astivo-autumnal parasite are rather rarely seen in the peripheral circulation.

The crescentic bodies: On the fourth to sixth days of any but initial paroxysms of the æstivo-autumnal infection the peripheral blood may contain red cells infected by spheroidal, oval, elliptical,

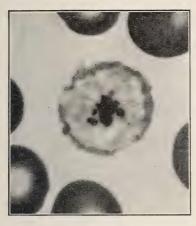


FIG. 7.—An Adult Tertian Parasite in the Same Stage as Fig. 6, with its Pigment Collected in a More Compact Manner at Its Central Part. The irregular dark zone at its periphery is the remains of the red blood corpusele in which the parasite has developed.



FIG. 8.—Completed Segmentation of a Tertian Parasite. Each of the dark rounded bodies represents a young parasite. The pigment of the parasite from which they are derived is shown, as well as the faint outlines of the red blood corpuscle in which they are contained.

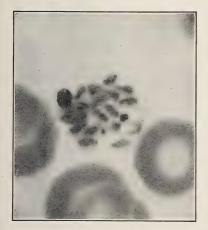


Fig. 9.-Same as Fig. 3.



FIG. 10.—A Young Parasite and an Adult Parasite with a Vacuole, in One Red Blood Corpuscle.



or small crescentic bodies which represent the early forms of the sexual cycle of the parasite. The relation of these forms to the young amœba is not clear. A remnant of hæmoglobin surrounds the crescent on all sides. The membrane or thickened outer border of the red cell is closely applied about the convex side of the crescent, while across the concavity it stretches loosely like a halter.

In the centre of the crescent is a sharply marked, light-blue staining or a chromatic area of variable size, containing the chromatin, and usually also the pigment.

The long persistence of crescents in the blood and their resistance to quinine are matters of common clinical observation.

Dr. J. H. Wright has kindly permitted the use of many of the accompanying photographs of the malarial parasites (see Plates V., VI., VII., VIII., and IX.).

Flagellate bodies: When blood containing crescents is allowed to stand in the air or under a cover-glass for a few moments some of the crescents slowly assume the spheroidal form, active vibratory oscillations of pigment granules begin, and soon, from one or more points, pseudopodia shoot out with active lashing movements. These flagella continue their movements for some time, changing their position actively, their shape slowly, while some may be seen to break off from the body and swim off through the plasma.

Tertian flagellate bodies develop from the full-grown tertian parasites in much the same way as from the crescents. Quartan parasites develop flagellate bodies very similar in appearance to those of the æstivo-autumnal type.

Exactly why and under what conditions it shows or fails to show these appendages is not known. They are about two or three times as long as a red corpuscle and one-sixth or one-eighth as wide. Sometimes there is pigment dotted along the flagellum itself, and then we can make it out more easily. Its distal end is especially apt to be pigmented, and by the help of this pigment we make out that it is bulbous, while similar swellings can sometimes be seen at other points along the flagellum (see Fig. 37). As the pigmented end is sometimes all that we can see of it, this gives rise to the appearance of a very small, actively locomotive pigmented body free among the corpuscles, and its course may be followed through several fields.

<sup>1</sup> McCallum has recently offered interesting evidence that they are sexual organs.



Fig. 37.—Flagellate Malarial Organisms. (After Manson's photographs.)

When the flagella have ceased moving, their presence is generally detected, if at all, by an irregular line of pigment dots about 20  $\mu$  long, which will be shown by careful focussing to be contained within a nearly transparent membrane.

Very often we find a leucocyte in process of closing round the flagellated parasite. Manson has lately succeeded in staining the flagellæ, and the accompanying photographs are from his stained specimens.

Pigmented leucocytes, containing the whole or part of malarial organisms or simply blocks or granules of black pigment, are usually to be found in the blood near the time of the chill. The pigment is to be carefully distinguished from the granules present in most leucocytes, which in certain lights look quite dark even if unstained, dark enough to be mistaken for pigment by the untrained eye. Careful focussing and changing the light will easily determine which we are dealing with, provided we are familiar with the appearances of leucocytes in the fresh unstained blood. In certain forms of the disease in which the organisms themselves retire to the internal organs, the presence of pigmented leucocytes may be the only evidence

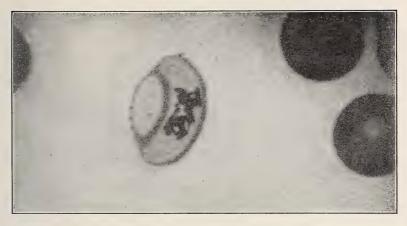


Fig. 11.—Crescentic Form of Æstivo-Autumnal Parasite in a Red Blood Corpuscle, which is Much Distorted by It. The pigment is seen in the centre of the parasite in the form of rods.

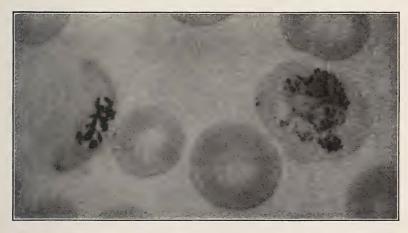
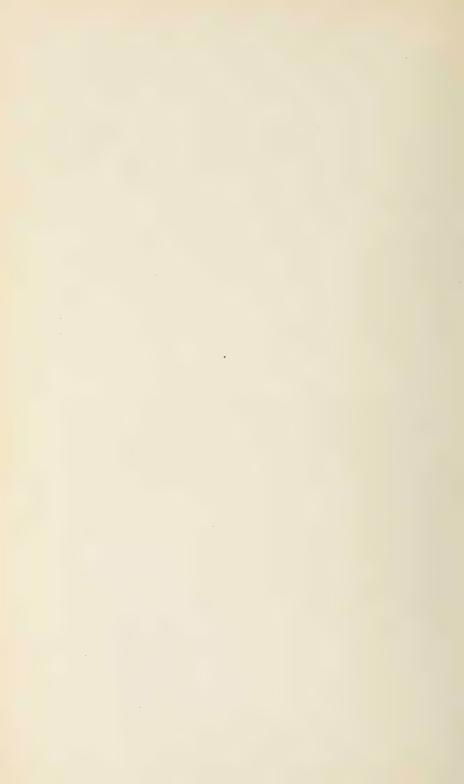


FIG. 12.—In the Right of the Figure is a Crescentic Parasite Distending a Red Blood Corpuscle. In this and Figs. 13 and 14 the blue-stained parasite is made to appear darker than the eosin-stained red blood corpuscles, by changing the character of the light used for illumination of the specimen. The deeper staining poles of the parasite is shown in this and the succeeding figures. In the left of the figure a tertian parasite in a red blood corpuscle is shown. There was, therefore, a double infection in this case.



of the disease to be found in the peripheral blood and is therefore of the greatest importance.

Hitherto I have spoken of the appearance of the parasites in the fresh unstained blood, this being by far the simplest, easiest, and surest way of finding them and the only way of studying their development. In cases in which we cannot make a microscopical examination at the bedside, we can sometimes preserve the organism alive between slide and cover-glass, until we can get it to the nearest microscope, even if this takes several hours. I have carried specimens in my handbag a whole morning and yet found the pigment of the malarial parasite in motion at the end of that time. Warm weather favors this. When it is necessary to keep the specimen some time before examination, it is best to paint on the slide a ring of vaseline or any gummy substance, and allow the drop of blood to spread out inside this ring so that the margins of the cover-glass are glued to the slide by the oily substance and the entrance of air is prevented. The cedar oil ordinarily used for immersion lenses answers the purpose very well. Both slide and cover should be gently warmed before the drop of blood is spread

Many physicians who cannot possibly carry a microscope about with them can easily find room for a few slides and cover-glasses, and they may be of great service.

When specimens have to be sent by mail, or for long distances, or in cold weather, we have to fall back on dried specimens prepared as described on page 43, provided always that a bedside examination is impossible. These can be stained by one of the following methods:

I. Leave the specimen for half an hour or more in equal parts of ether and absolute alcohol, dry them in the air, stain for from one-half to five minutes in a one-half-per-cent solution of eosin in sixty-per-cent alcohol, wash in water, dry and stain one-half to one minute in concentrated watery solution of methylene blue; wash again in water, dry in filter paper, and mount in Canada balsam. With this stain the nuclei of leucocytes and the malarial parasites are stained blue, while the red corpuscles are very pale yellow and almost transparent. This transparency of the red discs may be taken advantage of when the films either from accident or design are thick. The stained parasites can be recognized even if covered with a layer of red discs.

After drying thoroughly in the air the malarial parasite stains

best after fixation in ninety-five to ninety-seven per cent alcohol for fifteen to thirty minutes. The addition of ether to the alcohol secures no advantage (Ewing).

II. Thionin blue is a good malarial stain, especially for the young forms. Cover-glass films are to be fixed for one minute in a one-per-cent solution of formalin in ninety-per-cent alcohol, dried with filter paper, washed quickly in absolute alcohol, again dried with filter paper, and finally stained for thirty seconds in the following mixture, which should stand a week or more before it is used:

Yet on the whole I have had better success with the eosin and methylene blue despite its difficulties.

Modified Futcher and Lazcar method: "Fix the specimens five minutes in ninety-five-per-cent alcohol to 100 c.c. of which has been added, just before using, 1 c.c. of formalin. Stain one to three minutes in the following mixture: Saturated alcoholic solution of thionin, 20 c.c.; 20-per-cent carbolic acid, 100 c.c. The fixing solution must be used fresh, and the staining fluid must be at least one week old. The rings are then densely stained, and the specimens do not fade."

III. The ordinary Ehrlich triacid mixture with Hewes' afterstain gives good results. The organism itself stains blue with this mixture and stands out against the yellow of the corpuscle, the pigment looking as it does in the live parasite. It is sometimes convenient to use the same stain for the differential count and the malarial organism, as for instance when we have only one cover-glass preparation in a case of doubtful diagnosis. Fixing the specimen in alcohol and ether is here far better than heat; otherwise the technique is as above described under Triple Staining (page 44).

If the organisms are fairly numerous and the technique is good we can find them by this method even in preparations months old. In general, however, it is very inferior to the examination of the live organism in the fresh blood, and gives many more chances for error.

IV. Ewing states that he has never failed to secure a good result by the following procedure:

"1. To 1 ounce of polychrome methylene blue (Grübler) add 5

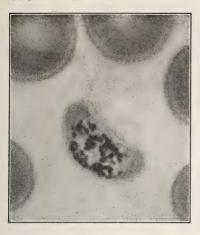


Fig. 13.—Crescentic Parasite Distending a Red Blood Corpuscle.



FIG. 14.—Ovoid Form of the Æstivo-Autumnal Parasite Distending a Red Blood Corpuscle. A portion of the corpuscle projects above the parasite and is much distorted. The dark line around the parasite also represents the remnants of the corpuscle.



Fig. 15.—Tertian Fever. Young form, socalled ring-body. Bloodplatelet on cell to left.



FIG. 16.—Tertian Fever. One so-called "ring" form; one matured organisms, the infested cell showing degeneration.



Fig. 17.—Tertian Fever. Maturing organisms with loosened-up chromatin. Large lymphocyte and platelets.



drops of three-per-cent solution of acetic acid (U. S. P., thirty-three per cent).

- "2. Make a saturated one-per-cent watery solution of methylene blue, preferably Ehrlich's (Grübler) or Koch's, dissolving the dye by gentle heat. This solution improves with age, and should be at least one week old.
- "3. Make a one-per-cent watery solution of Grübler's watery eosin.

"The mixture is prepared as follows:

"To 10 c.c. of water add 4 drops of eosin solution, 6 drops of neutralized polychrome blue, and 2 drops of one-per-cent methylene blue, mixing well. The specimens, fixed in alcohol, or by heat, are immersed, specimen side down, for one to two hours, and will not overstain in twenty-four hours. The density of the blue stain may be varied to suit individual preferences. The above proportions need not be rigidly followed, but the polychrome solution should be accurately neutralized, and the staining mixture should be deep blue."

Goldhorn has recently succeeded in digesting methylene blue with saturated solution of lithium carbonate so as to develop in it a large proportion of the red chromatin-staining principle. This fluid, neutralized by acetic acid, not only stains the chromatin rapidly (fifteen to sixty seconds), but demonstrates better than has yet been done early and extreme granular degeneration of the infected and other red cells. Goldhorn's fluid, ready for use, can be obtained from New York dealers.

So much for technique.

We often hear reports of fruitless search for the parasite in the blood of malarial patients, but the regularity with which they are found at all the larger hospitals and by all practised observers in this and other countries leaves no doubt that they are to be found in every case during some portion of the cycle. The practice of taking blood during a chill contributes, I believe, to the number of unsuccessful endeavors to find the organism; as mentioned above, this is the worst, not the best time to look for them. Too thick a layer of blood between slide and cover accounts for some failures, as I have found in personal experience.

No doubt, in many cases in which we fail to find the organism in supposed malaria a faulty diagnosis is the reason. Many of the

<sup>&</sup>lt;sup>1</sup> See Trans. New York Path. Soc., February, 1901.

cases in which latent malaria is supposed to have "come out" after a surgical operation are exploded by the negative examination for parasites and the positive indications of pus-pocketing which are afforded by a marked leucocytosis (never present in simple malaria), and the fact of insufficient wound drainage is often disclosed in this way. Whenever we see the leucocytes increased we begin to doubt the existence of an uncomplicated malaria; if, furthermore, we see no signs of any pallor of the corpuscles we doubt the presence of malaria still more, as there is no more rapid deglobularizer than the malarial organism.

How long after a chill the organisms may still be found in the peripheral blood is difficult to decide, but certainly they can be found any time within twenty-four hours after the last chill, unless quinine has been given, and sometimes even if it has been given.

### OTHER CHANGES IN THE BLOOD.

 $Red\ Corpuscles.$  —The following is from Thayer's remarkable monograph:

"A reduction in red corpuscles follows each paroxysm; these reductions are more marked after the early paroxysms than after those occurring later. When a certain degree of anæmia has been reached the losses per paroxysm are much less. When the number of corpuscles is reduced to 2,000,000 or 1,000,000 there is little tendency toward a further fall; sometimes there may be slight rises in the curve between the paroxysms; often, however, the number of corpuscles remains stationary for weeks.

"In pernicious cases the number of corpuscles may fall between paroxysms." Kelsch has seen the count decrease to as small a number as 500,000 per cubic millimetre. The diminution is greater the longer the disease lasts and the more intense its manifestations are

In Ewing's Montauk series, there were "no less than nineteen cases in which the changes of the progressive pernicious type had been established in a period not longer than ten weeks."

There can be no doubt that the tendency of the æstivo-autumnal parasite is to be massed in the bone marrow. The excessive demands on red-cell production render pernicious malaria an extremely favorable condition for this disturbance of the marrow and specific megaloblastic changes.

(AFTER GOLDHORN.)



FIG. 18.-Tertian Fever.



FIG. 19.—Tertian Fever. Marked stippling of infected corpuscle. Single chromatin body. Achromatic zone very distinct.

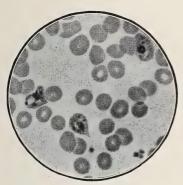


Fig. 20.—Tertian.

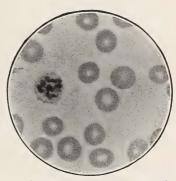


Fig. 21. — Intracorpuscular Segmenting Body in Tertian Fever. Stippling of corpuscle.

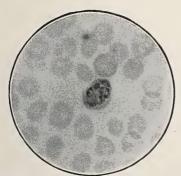


Fig. 22.—Segmentation of Malarial Organism in Tertian Fever. Stippling of corpuscle.



Fig. 23.—Tertian Fever. Double infection of corpuscle, one organism segmenting.



During the paroxysms, particularly the earlier ones, the red cells tend to *increase* in number.

In tertian and quartan fevers there is a rapid and almost complete restitution of the corpuscles during the afebrile period.

In æstivo-autumnal fevers the number of red cells bears a direct relation to the number of organisms. Crescentic bodies seem to have no influence on the number of red cells.

When after a paroxysm the number of corpuscles has been greatly diminished the succeeding paroxysm may be followed by a slight reduction only or even by an increase.

Bignami and Dionisi distinguish three types of post-malarial anæmia:

- 1. Ordinary secondary anæmia, but with leucopenia instead of leucocytosis; such cases usually end in recovery.
- 2. Anæmia practically identical with pernicious anæmia, megaloblasts being present, and ending fatally.
- 3. Anæmias which are progressive, because the bone marrow cannot compensate for the losses of corpuscles.

The rapidity of the diminution in red cells may be very great. Kelsch's count of 500,000 cells per cubic millimetre, mentioned above, was after thirty days' illness. Grawitz has seen a loss of 4,000,000 cells in six days.

Qualitative changes are those of severe secondary anæmia, deformities in size and shape, normoblasts, occasional megaloblasts in the worst cases, motility in the "pale, ghostly" cells.

Hæmoglobin.—The loss of hæmoglobin bears usually a direct relation to the number of parasites in the blood. As a rule, the corpuscles and hæmoglobin are diminished proportionally (color index = 1) but sometimes the hæmoglobin is reduced disproportionately.

In convalescence the restitution of hæmoglobin is often incomplete; persons living in malarial districts have often a slightly smaller percentage of hæmoglobin than those living elsewhere.

The rapid diminution in hæmoglobin is a valuable point in differential diagnosis between malaria and typhoid or pneumonia.

White Cells.—The number of leucocytes is usually subnormal, but a slight increase is shown at the beginning of the paroxysm. Following this increase there is a rapid decrease continuing throughout the paroxysm. The small number of leucocytes is to be seen at the end of the paroxysm when the temperature is subnormal. From

this time it shows a gradual increase until the beginning of the next attack (Billings).

In a general way the white cells follow the same course as do the red.

The differential count shows a lymphocytosis whenever the white cells are subnormal, the larger forms of lymphocytes being especially numerous, while the polymorphonuclear cells and eosinophiles are scanty.

In the severer æstivo-autumnal paroxysms Kelsch found that the leucocytosis of pernicious malarial attacks often consists in marked lymphocytosis; this was also observed by Ewing.

The extent of the leucocytosis varies between 10,000 and 35,000 cells, the latter having been observed by Kelsch shortly before death in a comatose patient.

In four cases of post-malarial anæmia Billings found quite marked leucocytosis.

The occurrence of pigmented leucocytes has already been mentioned.

Grawitz and others have noticed an increase of eosinophiles in post-malarial anæmia. I have frequently found small percentages of myelocytes, three per cent being the highest in my experience.

#### MALARIAL HÆMOGLOBINÆMIA.

During the paroxysms of this form of the disease, the number of the red cells is much diminished, rouleaux are not formed, marked poikilocytosis with nucleated forms is observed. The leucocytes are increased. The regeneration is very swift, twenty-four to forty-eight hours being usually sufficient to re-establish normal conditions.

### TYPHOID FEVER AND MALARIA.

"After the first week when the typhoid fever has become fully established, active sporulation of malarial parasites is extremely rare" (Ewing).

### CHAPTER XII.

## DISEASES DUE TO ANIMAL PARASITES.

#### FILARIASIS.

ALTHOUGH most commonly found in tropical countries, one species of the filaria sanguinis hominis is not very uncommonly found in various parts of the United States. Any case of chylous urine or elephantiasis should lead us to make a careful examination of the blood for the filaria. There are at least four species of filaria, one of which is present in the blood chiefly at night, another chiefly



Fig. 38.—The Filaria Sanguinis Hominis. The head, curled up, is seen at the right of the cut, the tail at the left. Instantaneous photomicrograph. Four hundred diameters magnification.

during the daytime, and another continuously. Only the filuria nocturna has thus far been seen in America (Fig. 38).

In examining for the filaria a slide of the fresh blood is prepared in the usual way, but after 8:30 o'clock in the evening, and examined at once. The embryo of this parasite (which is what we find in the human blood) is from one-ninetieth to one-seventieth of an inch in length, i.e., about fifty times the diameter of a red cell, and about the width of a red corpuscle. Seen in the blood it retains its vitality and motile power for a considerable time, so that its motions may continue a week or more between slide and cover-

<sup>&</sup>lt;sup>1</sup> In persons who sleep in the daytime and work at night the habits of the filaria are said to become reversed, so that it appears in the peripheral circulation chiefly in the daytime, and is to be looked for then.

glass. Cold has little effect upon it, even freezing temperature failing to do more than make the movements slower.

A distinction can generally be made out between the embryo proper and its sheath (see Fig. 39). From this sheath the embryo escapes when in the blood of the mosquito, which insect acts not infrequently as intermediary host and conveys the parasite indirectly from man to man through the medium of water. After suck-

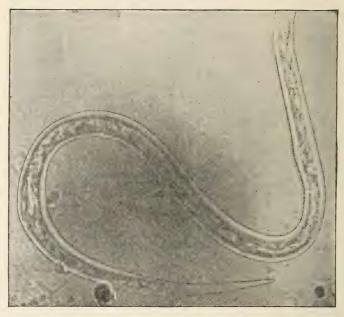


Fig. 39.—Tail of Filaria, Showing Prolongation of the Sheath beyond the End of the Embryo Itself. Magnified 800 diameters.

ing in the organism with the blood the mosquito lays its eggs and dies in some neighboring pond or stream whence the filaria again gains access to men.

It is a long, slender, snake-like, gracefully shaped worm, and when alive its activity is so great that measurements and observations of its structure cannot be made till it is paralyzed by approaching death (Fig. 40).

Posteriorly it tapers for one-fifth its length down to a very sharp point. The extreme end of the tail often looks as if articulated, for it does not harmonize with the general curve of the body,

but lies bent at an angle. Toward the head it tapers very slightly, and when alive a "pouting" movement as if of breathing can be seen at its very extremity. About the middle of the body a granular aggregation can be made out along the central axis of the animal. Except for this granular portion the parasite is so translucent that it is not easy to make it out at first. The distinction of body and sheath mentioned above appears as a "clear space" at each end of the body (vide Fig. 39). After the motions have ceased



FIG. 40.—The Movement of a Single Filaria during Four Successive Exposures of One-fifth of a Second Each, the Entire Series Occupying less than Five Seconds. Magnified 800 diameters.

it becomes darker and traces of transverse striation may be seen (Fig. 41).

It has no locomotive power and confines itself to wriggling in the same spot. Saussure says he has watched them "fighting with each other for hours."

The head of the filaria is said by some authorities to be supplied with feelers or flagella, and Manson describes what he calls a "cephalic armature" or fang (Fig. 42).

The same organism can sometimes be found in the chylous

<sup>1</sup> Philadelphia Medical News, June 28th, 1890, where he reports twenty cases seen in Charleston, S. C.



Fig. 41.—Head of Filaria. Shows structure and beginning granular degeneration. Magnified  $1{,}500~{\rm diameters.}$ 

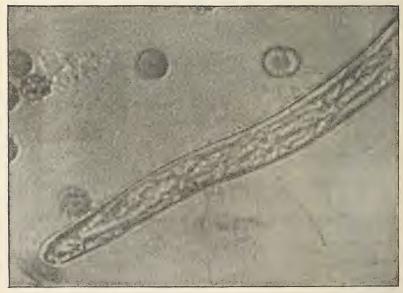


Fig. 42.—Head of Filaria Magnified 1,500 Diameters. The blur in front of the head may be due to the motion of flagella.

urine, but not every case of chyluria is due to the filaria sanguinis hominis. In a considerable portion of cases no such organism is to be found.

Henry' succeeded in staining the parasites *intra vitam* by giving the patient considerable doses of methylene blue internally for some weeks. Only a faint bluish tinge was imparted, however, to the organism by this method.

For finding the parasite it is best to use a low power, not an immersion lens, and the whole of several slides should be looked over.

Specimens can be dried and preserved for staining provided we

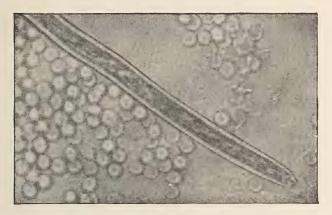


Fig. 43.—Head of Filaria Overlapping a Red Corpuscle. The appearance might be mistaken for the cephalic end of a sheath.

do not heat them over a lamp or pass them through a flame. Manson<sup>2</sup> stains with eosin and mounts in "glycerin jelly" (Fig. 43).

Several other species have been observed in England in negroes from the Congo River, but not hitherto in America. But as it frequently is to be found in persons who have no symptoms whatever, it may well be that some of these other species would be found here if one took the trouble to seek out natives of Southern China (one out of every ten of whom carries about the filaria in his blood), or of Central Africa, or other tropical regions.

<sup>&</sup>lt;sup>1</sup> Med. News, May 2d, 1896.

 $<sup>^{2}\,\</sup>mathrm{The}$  "Filaria Sanguinis Hominis," by Patrick Manson, M.D., Amoy, China, 1883.

### SPIROCHÆTE OF RELAPSING FEVER.

During the febrile paroxysms of relapsing fever, and for one or two days before them, Obermeyer and others have found constantly present in the peripheral circulation a parasite whose length averages about six times the diameter of a red corpuscle. Even under high-power lenses it is a mere thread in width, curled upon itself

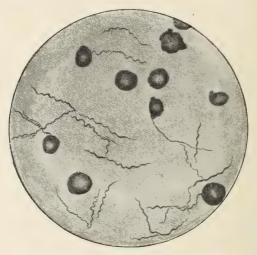


Fig. 44.—Spirochætes of Relapsing Fever in Human Blood.

like a corkscrew and actively motile, so that in examining the blood with a low power we get a "peculiar impression of disturbance" among the red cells.

The number of twists in this spiral-shaped organism varies a good deal, and one of its motions consists in contracting and extending itself like a spiral spring. It can thus multiply its own length three or four times. It has also a delicate, wavy, but rapid motion along its long axis. The whole thread, or a part of it only, may have these motions. Further, the whole parasite has power of locomotion apparently independent of the currents in the blood plasma of a slide and cover-glass specimen. Its locomotion is slow compared to the movements above described. Particularly in the blood post mortem they are apt to wind themselves into each other so as to seem much larger than they actually are, and sometimes

a large "nest" of them may look like a leucocyte, except for the fine wavy threads which can be seen in motion at the periphery of the mass.

The number present in the blood is very much smaller at the beginning of a paroxysm than after the second day. During the first few hours of a febrile period Mocyntkowsky could find only one spirochæte in ten or twenty microscopic fields, while later on he saw twenty or thirty of them in a single field. There are usually more parasites with each successive paroxysm.

Blood taken from different parts of the body often shows a great difference in the number of organisms to be found. The life history of a single parasite seems to be very short, but they multiply with the greatest rapidity. Albrecht has seen them so increase within six hours that whereas at first he saw only a few in the

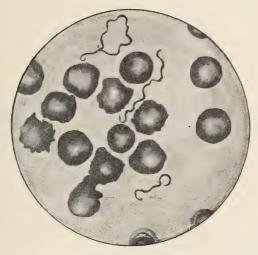


FIG. 45.—Spirochætes of Relapsing Fever in Human Blood.

whole slide he later found many in each field. As the spirochæte dies, its movements get languid, and finally it breaks up into small granular bits (spores?).

Between paroxysms the spirochætes are not found, but there are to be seen peculiar highly refractile globules compared by v. Jaksch to a diplococcus. The latter author believes that he has seen these develop into the spirochæte at the beginning of a paroxysm and hence believes them to be spores.

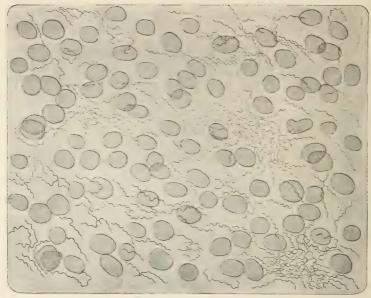
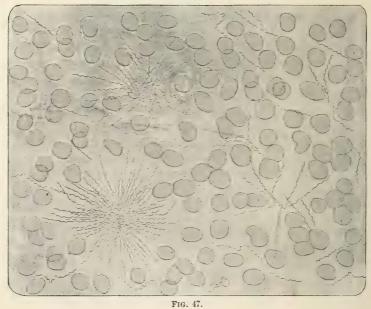


FIG. 46.



Spirochætes of Relapsing Fever.

This spirochæte is found in all cases of relapsing fever and in no other known disease, so that like the plasmodium malariæ it is pathognomonic and of the highest importance.

Anæmia and leucocytosis (during the paroxysm) are among the secondary results of the presence of this parasite in the blood.

Boeckman reported that the red cells sink during, and for one to two days after, the attack, increasing somewhat in the afebrile periods.

Laptschinsky, Heidenreich, and Boeckmann all noted considerable leucocytosis. Laptschinsky mentioned the presence of a very large number of coarsely granular leucocytes.

A certain resemblance has been noted between the spirochæte and a free flagellum broken off from a malarial parasite, but the clinical history and the presence or absence of other evidence of malaria in the blood would easily decide the question of diagnosis.

Technique of Examination.—As in looking for the malarial organism, it is best to examine the blood fresh between a slide and cover-glass (vide supra, page 7) and to use an oil-immersion lens. In dried specimens the organism can be stained with fuchsin, but it is much more difficult to recognize than in the fresh blood. The spirilla stain well with aniline



Fig. 48.—Leucocytes Containing Spirochætes.

dyes, and Karlinski succeeded in demonstrating flagella with some individuals. Concentrated solution of methylene blue stains all spirilla in two to five minutes. Phagocytosis (see Fig. 48) can easily be watched in the peripheral blood.

#### DISTOMUM H.EMATOBIUM.

Bilharz found this parasite post mortem in the large internal veins (portal, splenic, mesenteric, etc.), but as it has never been seen in the peripheral circulation its clinical importance is thus far *nil*.

#### ANÆMIA DUE TO INTESTINAL PARASITES.

The bothriocephalus latus, ankylostoma duodenale, and a few other parasites are capable of producing by their presence in the intestine a very severe anemia, which may be indistinguishable from pernicious anemia. Bothriocephalus anemia has been studied by Schaumann in a monograph (Berlin, 1894, Hirschwald) which is the very acme of careful, conscientious work and eclipses entirely the fragmentary observations of earlier writers. Ankylostomiasis has been thoroughly studied by B. K. Ashford of the United States army in Porto Rico, by Askanazy, Rogers, Sandwith, and others.

#### BOTHRIOCEPHALUS ANÆMIA.

The presence of the bothriocephalus latus in the intestine of man is usually accompanied by anæmia. In certain cases, however, under conditions not at all clear at present, there is produced an anæmia of the severest type, differing from ordinary pernicious anæmia only in its curability through the expulsion of the worm.

Schaumann's magnificent study of the blood of 38 cases resulted in the following data:

1. Red cells at time of first examination:

```
2,000,000 to 2,500,000 in 1 case (2,150,000)
1,500,000 " 2,000,000 " 9 cases
1,000,000 " 1,500,000 " 17 "
500,000 " 1,000,000 " 10 "
Under 500,000 " 1 case (395,000)

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38
Average of all = 1,290,000
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### 2. Hæmoglobin (first test):

- 3. Color index: Less than 1 in 8 cases (0.9 to 0.99), more than 1 in 30 cases. Average 1.09.
- 4. Average diameter of red cells 7.4 microns (slightly above normal).
- 5. Poikilocytosis marked, but its degree is not parallel with the degree of anæmia.
  - 6. Rouleaux formation always defective or altogether absent.
  - 7. Polychromatophilia and stippled red cells common.
- 8. Nucleated red cells present in all cases examined for them—26—but without parallelism with the degree of anæmia. Megaloblasts predominated in over half the cases. In 5 cases megaloblasts only appeared; in one case normoblasts only. In the other 20 cases both types were present. Mitoses were found in 2 cases.

Leucocytes usually normal or subnormal in number.

Differential count practically as in pernicious anæmia.

The eosinophiles are noted as "very scanty" in 25 cases and "apparently somewhat increased" in 1 case. [This is in sharp contrast with the eosinophilia usually present in ankylostomiasis (*vide* page 116.)] A few myelocytes were noted in 2 cases with leucocytosis.

Blood plates diminished.

So far the figures refer to untreated cases at the worst stage of the disease. Five-sixths of the cases were entirely and apparently permanently cured in about two months by the expulsion of the worms. Blood counts at the time of leaving the hospital showed:

```
In 3 cases about 2,500,000 red cells
2 " " 3,000,000 " "
2 " " 3,500,000 " "
16 " " 4,000,000 " "
4 " " 4,500,000 " "
4 " " 5,000,000 " "
```

Average 4,680,000 (16 cases still higher) with 70 per cent hæmoglobin.

Thirteen of these were followed up after discharge, and in these a full restitutio ad integrum occurred.

### ANKYLOSTOMIASIS (UNCINARIASIS).

The first careful observations of the blood of which I have knowledge are those of Zappert in 1892.' The following counts are reported by him:

		Per cent
Case.	Red cells.	Hæmoglobin.
1	5,180,000	50
2	4,384,000	40
3	4,350,000	50
4	4,272,000	30
5	3,728,000	45
6	3,372,000	40
7	3,272,000	25
8,	3,244,000	40
9	3,204,000	40
10	2,040,000	25
11	2,496,000	25

The most striking fact here is the low color index. The anæmia is of moderate grade.

Müller and Rieder<sup>2</sup> were the first to note the eosinophilia which later observations have shown to be so frequent. They record 8.2 per cent and 9.7 per cent in 2 cases of the disease. Zappert refers to 2 cases with 17 per cent of eosinophiles.

Rogers<sup>3</sup> compares the anemia produced by the ankylostoma with that due to malaria and with the blood of the average native of Assam, where his studies were carried on. His results are shown in the following table:

		,	
	Red cells.	White cells.	Hæmoglobin.
Healthy Assamese Chronic malaria. Ankylostomiasis.	2,000,000	7,325 1,600 5,338	67 per cent. 31 " 15 "

Rogers does not refer to the percentage of eosinophiles. In 1894 Bucklers<sup>4</sup> reported the following counts:

<sup>&</sup>lt;sup>1</sup>Zappert: Wien. klin. Woch., 1892, No. 24.

<sup>&</sup>lt;sup>2</sup> Müller and Rieder: Arch. f. klin. Med., vol. xlviii.

<sup>&</sup>lt;sup>3</sup>Brit. Med. Journal, 1900, p. 539.

<sup>&</sup>lt;sup>4</sup>Bucklers: Münch. med. Woch., 1894, No. 2.

	Case I.	II.	III.	IV.	v.	VI.
Red cells	3,649,000 13,000	15,000	3,954,000 20,600			
Hæmoglobin Eosinophiles	16%	4%	45.0% 53.6	10.4%	21% 22	25.0% 21.2
Polynuclear	46 37	74 22	22.3 25.1	$\begin{vmatrix} 46 \\ 43.6 \end{vmatrix}$	53 25	$   \begin{array}{r}     32.2 \\     46.6   \end{array} $

Leichtenstern (referred to by Ehrlich and Lazarus) illustrated the behavior of the eosinophiles in the presence of a secondary infection by this case:

"In the blood of a very anæmic, almost moribund patient with ankylostomiasis there were found, in 1897, 72 per cent of eosinophiles. The patient contracted a croupous pneumonia, and in the high febrile period of the disease the eosinophiles sank to 6 and 7 per cent, rising again after the termination of the pneumonia to 54 per cent. After removal of the worms the eosinophiles fell at once to 11 per cent.

"In 1898, when the fæces contained but very few ankylostomata . . . the eosinophiles amounted to 8 per cent."

At my request Dr. Bailey K. Ashford, first lieutenant and assistant surgeon in the United States army, has written the following account of his studies in the ankylostoma anæmias of Porto Rico. His results will soon be more fully reported in monographic form.

#### ANKYLOSTOMIASIS

BY BAILEY K. ASHFORD, M.D.,
FIRST LIEUTENANT, ASSISTANT SURGEON, U. S. A.

#### THE BLOOD IN GROSS.

The gross appearance of the blood in severe cases shows a great diminution in color and fluidity of the drop taken for examination. The statement that it resembles water in which fresh meat has been washed holds true in many instances. Under the microscope there is observed a great paucity of cellular elements and a frequent absence of rouleaux.

### QUANTITATIVE CHANGES.

### Red Corpuscles.

There is a progressive tendency to profound oligocythæmia, even to as great an extent as is found in severe cases of pernicious anæmia, and to an even greater oligochromæmia.

Eighteen cases were examined in Ponce, Puerto Rico, at the field hospital for storm sufferers of August 10th, 1899. Of the eighteen cases the average count was 1,776,176 red cells per cubic millimetre on admission; the lowest recorded was 668,888, and the highest was 3,084,440 per cubic millimetre, both these counts having been taken after three weeks' observation; 10 cases on admission gave counts ranging from 1,000,000 to 2,000,000; 7 cases between 2,000,000 and 3,000,000; one case fell below 1,000,000.

Sandwith studied in Egypt 173 cases. Of these only 3 exceeded 4,000,000 red cells per cubic millimetre; twenty-three per cent were found to have between 3,000,000 and 4,000,000; 46.8 per cent lay between 2,000,000 and 3,000,000, and 28.3 per cent had less than 2,000,000. His minimum count was 930,000, and his average count of hospital cases was 1,290,000 per cubic millimetre.

Counts as low as 500,000 have been recorded. In my series the abrupt rise and fall in blood count was astonishing, and error could hardly have been made, as the two counts which were made at each examination tallied very closely in each instance. Three cases giving respectively 1,200,000, 1,484,440, and 1,600,000 fell in about three weeks to 801,104, 687,776, and 668,888 red cells per cubic millimetre. Two rose from 697,776 and 2,064,664 to 2,664,440 and 3,084,440 per cubic millimetre.

We must make allowances for intensity of infection, virulence of infection, immunity, etc., but ordinarily the red blood count in typical cases will present from 1,500,000 to 2,500,000 per cubic millimetre. Some of the Puerto Rican cases demonstrate a severe type of the disease, and notes of other cases there show that counts nearer 1,000,000 are frequently encountered.

This tremendous loss of blood is seemingly well borne for a longer period than one would expect, and men with one-fourth their normal quota of red blood corpuscles subject themselves to quite hard labor.

### White Corpuscles.

There is probably no true leucocytosis in the disease. As it is an affection liable to be complicated by other diseases producing leucocytosis, we can easily explain many of the classical references to the "leucocytosis of ankylostomiasis." An examination of the chart of the Ponce cases will show this more plainly.

The average number of white corpuscles in these cases was about 7,000 per cubic millimetre. One case with lobar pneumonia had 18,000 leucocytes per cubic millimetre, and another with abscess of the liver had 11,000. Excepting one case (with 12,700), all the rest were well below 10,000, and the average of 17 uncomplicated cases was about 6,000. The lowest record was 1,500 per cubic millimetre.

### Hæmoglobin.

The hæmoglobin is more reduced than the red blood count. In Sandwith's cases the hæmoglobin average was 26 per cent. The average of 18 of the Ponce cases gave about 21 per cent of hæmoglobin and an average color index of 0.62 for 17 of them. The lowest reading was 10 per cent, the highest 30 per cent. Twice only the color index rose above 1.0; once to 1.43, and once to 1.09.

### QUALITATIVE CHANGES.

# (a) Red Corpuscles.

Poikilocytosis was present in 16 of 17 of the Ponce cases. Macrocytes are exceedingly common in this disease, as are also microcytes, and the deformities of the cells in advanced cases are as varied and as frequent as in pernicious anæmia.

Polychromatophilia was marked in only 4 cases, but irregularity in staining is a prominent sign.

# Normoblasts and Megaloblasts.

Normoblasts and megaloblasts are apparently not so frequently met with as in pernicious anæmia, and there is seldom a case reported as having a preponderance of the latter. Among the Ponce cases only one patient presented an equal number of each. The

<sup>1</sup> The von Fleischl apparatus was used, and the capillary tube was three times filled that chances of an error might be minimized.

average number of normoblasts per cubic millimetre was about 35; of megaloblasts, about 7. Five cases had no normoblasts and 12 had no megaloblasts, while 5 had neither.

### White Corpuscles.

In the differential count the polymorphonuclear neutrophiles gave an average of 63 per cent. The lowest noted was 40 per cent, and the highest 74 per cent. The normal was not disturbed save when the percentage of eosinophiles rose; then that of the polymorphonuclear neutrophiles sank proportionately to the rise in the former. As seen by the chart of the Ponce cases, addition of the percentages of the two varieties gives us a normal polymorphonuclear neutrophile count.

There was no lymphocytosis noted. The average was about 19 per cent for small lymphocytes and 7.5 per cent for the large variety.

The eosinophiles show a remarkable increase in some cases and some increase in nearly all. The average eosinophile count in the Ponce cases was 10.3 per cent; 6 showed a percentage at or below 4. The highest was 40 per cent, the lowest 1\frac{1}{4} per cent. Three were respectively 13, 31, and 40 per cent.

Atlas, of Vienna, reports a case with 16 per cent of eosinophiles, and Kwasnicki, of Galicia, one with 24 per cent of these cells. The polymorphonuclear neutrophiles in each instance were respectively 51 and 49 per cent of the total differential count.

These facts would seem to suggest (1) that the blood in this disease is modified by some toxin, as post-hemorrhagic anæmia has not this characteristic of eosinophilia, and trichiniasis, a disease due to another nematode parasite, has. Indeed, it was this eosinophilia and the coincidence of the discovery of high eosinophilia by Brown, of Johns Hopkins University, in the first-named affection that led the writer to suspect an animal parasitic origin in the cases of anæmia at Ponce.

(2) That these cases had presented at some period of the infection a higher eosinophilia, especially those bearing a lower percentage. The cases with the three higher counts were of comparatively acute character.

Myelocytes are occasionally reported, a notable case being that of Blickhahn, <sup>10</sup> of St. Louis, Mo. One of the Ponce cases showed a few.

Schedule of Blood Examinations in Nineteen Cases at Ponce, Porto Rico.

Date.	Current number.	Red cells.	Percentage of hæmoglobin.	White cells.	Percentage of poly- morphonuclear leucocytes.	Percentage of small leucocytes.	Percentage of large leucocytes.	Percentage of eosinophiles.	Normoblasts per cubic millimetre.	Megaloblasts per cubic millimetre.	Remarks.
Nov. 4th Nov. 23d	1	1,530,116 1,880,000	20 16	6,800	65	21	9	5	26	13	Poikilocytosis, Polychro- matophilia, many micro- cytes and macrocytes.
Nov. 3d Nov. 23d	2	697,776 2,664,440	20 23	7,960	59	17	15	9	144	46	Poikilocytosis. Polychro- matophilia, many macro-
Nov. 4th Nov. 23d	3	1,533,112 1,973,328	22 23	2,000	64	22	8	6	8		cytes and microcytes. Poikilocytosis. No rou- leaux.
Nov. 5th Nov. 23d	4	1,200,000 801,104	15 17	4,200	64	23.4	6	6.6	109	8	Poikilocytosis. Polychro- matophilia.
Nov. 23d Nov. 23d	5	1,484,440 687,776	10 14	6,000	64	24	8	4	12	••	Poikilocytosis. Slight ten- dency to rouleaux forma- tion; macrocytes and microcytes, latter pre- dominate over former.
Nov. 6th	6	2,193,328	23	8,800	65	26	8	11/4	123	35	Poikilocytosis. No ten- dency to rouleaux for-
Nov. 7th	7	1,633,328	17	5,600	60	23	5	12	11		mation.  Poikilocytosis. Many macrocytes and microcytes; slight rouleaux formation; marked chromatophilia.
Nov. 7th	8	2,064,664	23	4,800	74	17	6	3	28		Poikilocytosis. Rouleaux
Nov. 23d Nov. 7th Nov. 23d	9	3,084,440 1,271,104 2,520,000	31 14 24	7,800	60	17	6	17	30	15	formation good.  Has elephantiasis Arabum, but I cannot identify the filaria as yet. Micro- cytes predominate over macrocytes. Good rou- leaux formation.
Nov. 7th	10	1,600,000	17	1,500	72	20	4	4	6		Poikilocytosis.
Nov. 23d Nov. 8th Nov. 8th	12	668,888 1,800,000 2,296,656	13 25 30	4,600 7,680	69 52	22 26	7 12	$\begin{bmatrix} 2 \\ 10 \end{bmatrix}$	9		Poikilocytosis.
Nov. 9th	13	1,268,888	20	6,800	63	17	7	13	• •	• •	Poikilocytosis. Rouleaux formation good.
Nov. 9th	14	2,440,000	25	11,000	50	10	9	31			Poikilocytosis. Rouleaux formation slight; has abscess of liver.
	15 16	2,353,328 2,934,444	17	12,700 5,200	73 72	17 20	4 5	6 3	iö	iö	Poikilocytosis. Rouleaux. Tertian malarial parasites
Nov. 10th.	17	2,140,000	231⁄2	18,000	40	12	8	40	36		found. Rouleaux good. Poikilocytosis. Rouleaux good. I believe this man to have been suffering from pneumonia at time
Nov. 12th.	18	Unknown.	30	9,000	60	16	10	10	125		of examination. Poikilocytosis. Rŏuleaux formation good.
Nov. 20th.	19	1,560,000	16	2,400	72	10	5	13			Tormanon good.

The course of the convalescence is remarkable for its brevity in acute cases, but when serious secondary affections are engrafted on the original disease it is very slow. The chief difficulty seems to result from damaged intestine and heart. One of the writer's patients at the beginning of treatment was in imminent danger of

succumbing to the anæmia. He was a boy of about ten years of age and his case acute. Within six weeks he was transformed into as ruddy a specimen as could be expected, on the administration of the usual thymol treatment.

Of Sandwith's 173 cases he states that the least gain on treatment was 310,000 red cells per cubic millimetre. Another case, that of a boy, gained in one month seven pounds in weight and 2,208,000 red cells per cubic millimetre. Ten patients gained over 2,000,000, one of them 2,542,000. His average gain of all cases in hæmoglobin was 22 to 32 per cent.

Agnoli<sup>11</sup> reports a case in which there was a gain of 2,168,000 red cells per cubic millimetre and of twenty-six pounds in weight in thirty-five days.

#### AUTHORS CITED.

- 1. Daniels: The British Guiana Medical Annual, 7th issue, 1895.
- 2. Bevan Rake: Journal of Pathology, November, 1894.
- 3. Lussano: "Contributo alla patogenesi dell' anemia la anchylostomiasi." Rivista Clinica, 1890, No. 4.
- 4. Arslan: "L'anemie des mineurs chez les enfants." Rev. mens. des mal. de l'enf., 1892, p. 555.
- 5. Bohland: "Über die Eiweisszersetzung bei der Anchylostomiasis." Münch. med. Wochenschr., 1894, No. 46.
- 6. Sandwith: "Observations on Four Hundred Cases of Anchylostomiasis," written for the 11th International Med. Congress at Rome, 1894.
- 7. Atlas: "Anchylostomum Duodenale." The Med. Press and Circular, November 14th, 1894.
- 8. Kwasnicki: Article published in the Przeglad Lekarski, October 15th, 1899.
  - 9. Scheube: Extracts from a work on tropical diseases.
  - 10. Blickhahn: Med. News, December 9th, 1893, Philadelphia, Pa.
- 11. Agnoli: "Consideraciones sobre dos casos de anemia por Ankylostoma Duodenal." La Cronica Medica, Lima, Peru, 1893, vol. x., p. 6.

FORT SLOCUM, N. Y., March 23d, 1901.

#### TRICHINOSIS.

In March, 1896, a case of trichinosis entered Professor Osler's wards at the Johns Hopkins Hospital. The study of the blood of this case by Thomas R. Brown was the means of calling the attention of the profession for the first time to the value of blood examination in the diagnosis of trichinosis. The blood was examined daily for over two months. The total leucocyte count gradually rose from 17,000 at entrance to 35,700 forty-four days later. Thence it de-

clined until, on the sixty-eighth day, it was 11,000. The eosino-philes were 37 per cent (6,300 absolute) at entrance, and rose with the total count until a percentage of 54 (19,500 absolute) was reached on the forty-fourth day (when the total leucocytes were 35,700). The highest percentage, 68.2, was reached on the forty-ninth day, when the leucocytes were 17,700 (eosinophiles 11,070 absolute). On the sixty-eighth day (the date of discharge) the eosinophiles were 68 per cent (1,850 absolute).

[For the daily counts of this splendidly studied case see p. 484.] A year later Brown studied a second case. His examinations showed as before a very marked eosinophilia (see table LXIX.).

TABLE	LXIX.	-Case	IIB	LOOD	CHART.

DATE.	Leuco-			F THE V			L NUMBE FORMS P		
	cytes.	P. N. Neut.	L. M. and T.	S. Monos.	Eos.	P. N. Neut.	S. Monos.	L. M. and T.	Eos.
April 15th	13,000	43.1	6.5	1.4	42.8	5,600	180	840	5,560
16th		47.7	4.7	4.5	39.1				
17th		52.0	2.8	7.6	37.6				
18th	8,000		2.0		22.0				
19th		57.2	2.8	8.0	32.0	4 000	4 000	0.40	
20th	8,900	55.2	3.8	11.2	31.8	4,900	1,000	340	2,830
21st	8,700	<b>~</b> 0.0	0 m		000	0.000	4 050	200	2 000
22d	10,700	58.0	2.7	11.7	27.7	6,200	1,250	290	2,960
23d	6,000	56.2	2.0	15.2	26.2	3,370	910	120	1,570
24th	11,000	60.4	4.0	13.2	22.4	6,640	1,450	440	2,460
25th	11,000	57.2	4.2	18.6	20.0	6,290	2,050	460	2,200
26th	9,600	60.7	5.3	12.3	21.7	5,830	1,180	510	2,080
27th	11,300	63.0	5.0	17.0	14.7	7,120	1,920	560	1,660
28th	12,700	62.7	4.0	17.0	16.3	7,960	2,160	510	2,070
29th	12,000	67.0	3.25	15.25	14.0	8,040	1,830	390	1,680
May 1st	10,700	58.3	4.0	22.0	15.7	6,240	2,350	430	1,680
3d	13,000	64.3	4.0	16,0	15.7	8,360	2,080	520	2,040
5th	12,000	64.7	4.0	16.0 16.4	15.3	7,760	1,920	480	1,840
7th	9,300	62.8	4.0		16.8 20.0	6,140	1,530	370	1,560
10th	10,700	60.4		16.4		6,460	1,750	300	2,140
12th	11,000	60.4	3.3	16.6	19.6	6,640	1,820	360	2,160
14th	12,000	58.8	2.8	18.8	19.6	7,060	2,260	340	2,350
17th	9,000	58.8	3.6	20.0	17.6	5,290	1,800	320	[1,580]

Brown's third case was studied in December, 1897.

The blood (Table LXX.) on admission showed 45 per cent of eosinophiles, and this, as in the two previous cases, led to the diagnosis of trichinosis and the subsequent confirmation of that diagnosis by the removal of a portion of muscle and the discovery of trichinæ therein.

TABLE LXX.—CASE III.—BLOOD CHART.

Date.	Red blood corpuscles.	Leuco- cytes.	Per cent polymorpho- nuclear neutrophiles.	nuclears and	Per cent small mono- nuclears.	Per cent eosino- philes.
Dec. 22d 23d 27th	4,700,000 4,300,000 4,546,000	17,000 15,300 12,000 14,700  13,000 9,000	48.4 52.7 42.4 42.2 31.6 32.4 35.2 45.5	4.7 3.6 4.0 4.2 4.4 3.0 4.0 2.0	1.5 3.1 5.6 4.6 19.0 21.8 23.4 17.7	45.4 40.4 45.0 49.0 44.6 42.8 37.2 34.7

This case was seen subsequently (July 10th, 1898) six months after the disappearance of all symptoms, and the following (normal) count was registered.

The count made on July 10th, 1898, was:

Leucocytes (per c.mm.)	7,000	
Polymorphonuclear neutrophiles	68 per cer	ıt
Small mononuclears	23 "	
Large mononuclear and transitional forms	6 "	
Eosinophiles.	3 "	

A fourth case was reported by the same writer in January, 1899 (Medical News). The counts were as follows:

Date, 1898.	Leuco- eytes.	Per cent polymorpho- nuclear neutrophiles.	Per cent small mono- nuclears.	Per cent large mononu- clears and transitionals.	Eosino- philes.
August 8th  10th 13th 28th September 4th 18th 25th October 2d November 5th 13th 20th	18,100 8,200 7,900 9,600 8,750	48 45 49 55.2 61.5 54 49 64.5 61	7.3 14.5 18.5 19.6 16 19.5 40 27 27	1.7 2 2.5 2 2.5 2 2.5 2.5 2.5 4.5	48 48 38.5 30 23.2 20 24 8.5 5.5 7.5

In January, 1900, Blumer<sup>1</sup> and Neumann report a "Family Outbreak of Trichinosis" including nine cases. The counts were as follows:

<sup>&</sup>lt;sup>1</sup> American Jour. Med. Sciences.

1	Name.	Date.	Leuco- cytes.	Per cent polynu- clears.	Per cent transi- tionals and large mo- nonuclears.	Per cent small mononu- clears.	Per cent eosino- philes.
Case 1.	D. V	March 8th 13th	19,000 18,000	47.4	8.8	3.2	40.6
		19th 26th April 1st	12,400 20,600 13,200	50.6 69.6 73.0	4.4 5.6 5.0	7.6 10.0 12.0	$37.4 \\ 14.8 \\ 10.0$
Case 2.	Mary C	March 8th 12th 19th 26th April 1st	8,400 20,000 17,200 12,000 16,000	61.4 51.6 39.0 48.0 42.0	6.8 10.4 4.8 6.6 4.3	10.0 14.6 16.2 14.6 12.2	21.8 23.4 40.0 30.8 41.5
Case 3.	A. V	March 8th 12th 19th 26th April 1st	24,000 14.000 20,600 18,000 15,200	56.8 52.4 64.4 66.25 56.6	6.4 3.8 2.8 4.0 4.4	3.6 7.8 5.2 6.5 10.4	33.3 36.0 27.6 23.25 28.6
Case 4.	Mrs. D. V.	March 8th 12th 19th 26th	8,000 12,400 13,200	51.0 50.8 50.6 54.0	7.8 4.2 5.6 5.0	7.6 18.0 11.0 11.0	33.6 27.0 32.8 30.0
Case 5.	T. V	March 8th 12th 19th 26th	8,000 14,000 18,600 14,600	32.6 49.0 41.4 35.0	10.8 4.2 5.6 3.5	$\begin{array}{c} 6.4 \\ 15.0 \\ 10.8 \\ 18.5 \end{array}$	50.2 31.8 42.2 43.0
Case 6.	R. G	March 9th 19th 26th April 9th	14,000 17,200 8,000 6,000	45.6 $45.4$ $48.8$ $64.4$	15.16 2.6 5.0 6.8	$\begin{array}{c} 7.0 \\ 6.0 \\ 10.8 \\ 12.2 \end{array}$	32.16 $46.0$ $35.4$ $16.6$
Case 7.	J. V	March 12th 19th 26th April 1st	16,000 23,000 16,600 8,600	44.0 53.2 41.6 39.3	9.2 2.8 6.0 9.0	15.8 6.2 13.0 16.1	31.0 37.0 39.4 35.6
Case 8.	R. V	March 12th 19th 26th April 1st	$10,000 \\ 14,600 \\ 12,600 \\ 12,600$	39.0 36.0 55.5 44.0	6.0 4.8 5.5 7.0	20.0 8.5 9.25 5.5	$\begin{array}{c} 35.0 \\ 50.4 \\ 29.75 \\ 38.0 \end{array}$
Case 9.	Mrs. R. G.	March 9th 19th 26th April 9th	$12,400 \\ 15,200 \\ 12,600 \\ 10,000$	$48.0 \\ 59.2 \\ 67.0 \\ 74.0$	9.6 4.0 6.5 5.0	25.4 16.8 13.0 13.0	17.0 20.0 13.5 8.0

# My own experience is as follows:

Case.	Date.	Red cells.	White cells.	Per cent hæmoglobin.	Per cent polynuclear.	Per cent lymphocytes.	Per cent eosinophiles.	Per cent mast cells.	Per cent myelocytes.
2	September 30th, 1897. November 4th. September 6th, 1899. 10th. 13th. 15th. 19th. 22d.	5,120,000 4,900,000	11,000 7,000 1,410 25,000 23,000 21,000 11,000 14,000		39.0 36.5 59 71.2	31.0 46 3 7	28.0 17 34 19	2.0 2.5 2	2.0

Case.	Date.	Red cells.	White cells.	Per cent hæmoglobin.	Per cent polynuclear.	Per cent lymphocytes.	Per cent eosinophiles.	Per cent mast cells.	Per cent myelocytes.
2	September 29th November 4th 10th	4,712,000	10,900	70	71.2 53.6 58.9	9.6 23 32	16 23 9.1	2.0	1.2
3	29th First day Fourth day Seventh day	5,728,000	15,600 11,600 10,500	•••	67.8 65 60 75	24.4 11 16 18	7.8 22 24 7	1.4	6
	Tenth day Thirteenth day Fifteenth day		13,200 16,100 15,200	::	39 52 39	23 13 37	37 35 23	.6 1	4
4			17,900		54	22	24		

Atkinson' reports one case as follows:

Date.	Red cells.	White cells.	Per cent hæmoglobin.	Per cent polynuclear.	Per cent lymphocytes.	Per cent eosinophiles.
January 14th, 1899. 18th. 25th. 31st	5,528,000	28,000	93	31.1 21.5 25.6 43.4	9.5 24.2 39.4 16.6	58.5 54.3 35 40

Gwyn² reports a similar case in which the eosinophiles ranged from 33 to 65.9 per cent during a period of six weeks. The leucocytes were at one time 17,000 per cubic millimetre.

Stump<sup>3</sup> found 52 per cent of eosinophiles in his case.

W. W. Kerr<sup>4</sup> puts the following figures on record:

	Date. 1899.	Red cells	White cells.	Per cent hæmo-globin.	Per cent polynuclear.	Per cent small lympho- cytes.	Per cent large lympho- cytes.	Per cent eosino-philes.
Case 1	Nov. 9th 10th 11th	5,800,000 4,888,000	25,000 20,600	85	52.0 49.4 53.6	1.0 3.6 5.9	1.0 2.8 2.2	42.0 44.2 38.3
	13th 15th				41.7 36.6	$\frac{4.3}{7.7}$	3.2	54.0 52.0
	16th 17th		13,000		35.0 47.0	5.3 8.5	7.6 15.5	52.5 29.0
·	18th				46.5	10.5	10.9	31.1

<sup>&</sup>lt;sup>1</sup> Phila. Med. Journal, June 3d, 1899.

<sup>&</sup>lt;sup>2</sup> Centralbl. f. Bakt., vol. xxvi., No. ii.

<sup>&</sup>lt;sup>3</sup> Phila. Med. Journ., June 17th, 1899.

<sup>&</sup>lt;sup>4</sup>Phila. Med. Journal, August 25th, 1900.

	Date. 1899.	Red cells.	White cells.	Per cent hæmo- globin.	Per cent polynuclear.	Per cent small lympho- cytes.	Per cent large lympho- cytes.	Per cent eosino philes.
Case 1	Nov. 20th				48.0	8.0	8.0	34.0
case	22d			· ::	50.8	2.0	14.0	32.0
	23d				52.4	10.9	6.8	. 38.3
	$27 \mathrm{th}$				40.0	15.0	4.0	41.0
	$29 \mathrm{th}$	4,250,000	10,000	100	22.5	19.8	14.6	43.0
	Dec. 3d				28.7	2.8	10 6	57.8
	8th				10.6	6.0	14.8	68.7
	11th				23.6	13.2	14.3	48.9
	13th			• • •	23.9	9.8	5.6	60.7
Case 2	Nov. 17th				41.6	16.4	23.9	18.1
00000 1011	18th				53.2	18.9	6.0	21.9
	20th				37.0	11.0	6.0	45.0
	21st				34.0	11.0	4.0	50.0
	22d				20.0	8.2	3.2	68.0
	23d			.,	15.3	5.7	2.1	76.9
	$24 \mathrm{th}$				10.4	7.2	1.4	81.0
	$25 \mathrm{th}$				10.5	6.4	2.4	80.7
	27th	3,340,000	20,000	77	17.0	6.4	9.1	66.9
	29th				6.5	3.9	8.4	81.2
	Dec. 1st				4.2	3.0	6.1	86.6
	2d				11.4	10.1	4.9	73.5
	3d				10.0	7.3	6.1	76.6
	5th	,			14.8	8.0	7.0	70.2
	$6 \mathrm{th}$		1	٠	0:75	5:0	18.8	76.0
	8th				3.1	9.5	8.6	78.8
	$9 \mathrm{th}$				10.9	3.6	9.0	72.7
	11th				11.2	18.2	14.2	56.4
	13th	3,300,000	17,000		13.1	9.4	9.3	68.2

Harlow Brooks¹ examined the blood in one case, and found at the time of admission to the Bellevue Hospital (February 2d, 1900) 18,000 leucocytes, with 10 per cent of eosinophiles; on February 12th, 1900, 44 per cent of eosinophiles; thence a steady increase up to 83 per cent, followed by a decline, until on March 14th 15 per cent of eosinophiles was present. Many of the granules wer smaller than those of normal eosinophiles, but there was no evidence of forms transitional between eosinophiles and neutrophiles.

F. P. Kinnicutt<sup>2</sup> reported a similar case, and H. C. Gordinier<sup>3</sup> mentions two, one presenting 77 per cent, the other 29.9 per cent of eosinophiles.

<sup>&</sup>lt;sup>1</sup> Med. Record, May 19th, 1900.

<sup>&</sup>lt;sup>2</sup> Practitioners' Soc., February 2d, 1900.

<sup>&</sup>lt;sup>3</sup> Medical Record, October 20th, 1900.

### Summary.

From the total of counts in cases here assembled the constant presence of eosinophilia in trichinosis may safely be inferred.

### Diagnostic Value.

The characteristic blood lesions change trichinosis from the position of a disease very difficult and uncertain of diagnosis (without excision of a bit of muscle) to one whose recognition is usually easy. Cases formerly diagnosed as typhoid, muscular rheumatism, or neuritis now find their true interpretation.

#### Other Intestinal Worms.

Bücklers, working under Leichtenstern's direction, has recorded the following data in cases affected with various more or less inoffensive worms:

#### I. Anguillula Intestinalis.

	Per cent.
Eosinophiles	. 13.5
Polynuclears	. 38.5
Lymphocytes and transitional	. 48

### II. ANGUILLULA INTESTINALIS WITH ANKYLOSTOMA.

	Per cent.
Eosinophiles	. 15
Polynuclears	. 58
Lymphocytes and transitionals	. 27

#### III.

	Case I.	Case II.	Case III.	Case IV.
	Oxyuris and ascarides.	Oxyuris.	Oxyuris with ascarides and trichocephalus.	Oxyuris with ascarides, trich- ocephalus and Tænia saginata
Eosinophiles	19 per ct. 53 "	16 per ct. 63 "	8 per ct. 69 "	5.7 per ct. 63.3 "
sitionals	28 "	21 "	23 "	31.0 "

#### IV. ASCARIDES (alone).

The report of the Jenner Hospital at Berne (1890) includes the account of a case in which ascaris was present in large numbers. The blood showed but 2,480,000 red cells before the expulsion of the parasite by santonin; two weeks later the red cells were 4,200,000.

V. Tænia (Bücklers).

Eosinophiles Polynuclears Lymphocytes and transitionals	49.4 "	Case II.  Tænia Saginata.  5.5 p. ct. 65.0 "  29.5 "	Case III.  Tænia Nana.  7.0 p. ct. 42.0 "  51.0 "	Case IV. Tænia Saginata. 5.0 p. ct.	Case V. Tænia Saginata.  10.0 p. ct.
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### CHAPTER XIII.

### DISEASES OF THE SKIN.

#### DERMATITIS, HERPETIFORMIS.

According to Leredde, who has written extensively on the condition of the blood in this disease, the following terms are in use to designate the same actual set of facts: Dermatitis herpetiformis; Dühring's dermatosis; Polymorphous pruriginous dermatitis; Hydroa (Unna); Pemphigus vegetans (Neumann); Hallopeau's infectious dermatosis; Herpes gestationis.

In all of this he finds marked constant eosinophilia, averaging 16 per cent. At times the percentages may reach 25 or 30.

My own experience includes three cases, one diagnosed as dermatitis herpetiformis, the others as hydroa æstivale. The counts were as follows:

	Case I. Dermatitis herpe- tiformis.	Case II. Hydroa æstivale.	Case III. Hydroa æstivale.
Polynuclear neutrophiles Small lymphocytes Large lymphocytes Eosinophiles Myelocytes	8 " " 19 " "	40.0 per cent 42.4 " " 8.6 " " 8.2 " "	34 per cent 43 " " 8 " " 15 " "

Brown' reports the following figures in a case of dermatitis herpetiformis (twenty-seven years' duration):

			1		
	June 12th, 1899.	June 17th, 1899.	June 25th, 1899.	June 30th, 1899.	Sept. 5th, 1899.
Red cells				5,163,000 9,000	5,808,000 9,700
Polynuclear neut	38.0	Per cent. 31.3 24.4 44.3(!)	Per cent. 29.25 34.5 36.25	Per cent. 39.25 21.5 39.25	Per cent. 36.0 34.4 29.3

<sup>&</sup>lt;sup>1</sup> Soc. for Original Research, Conn., October 12th, 1899.

#### ERYTHEMA.

No.	Age.	Red cells.	White cells.	Per cent hæmo- globin.	Remarks.
1	29		19,700		First day. Temperature 102°; erythema nodosum and multiforme.
			$20,400 \\ 12,900$		Second day. Temperature 103°.   Sixth day. Temperature 98°.
2	27		18,400		Temperature 104°.
			6,800		Temperature 104°, third day. Eosinophiles not +.
3	18		11,400	65	Nodosum.
4	17		8,200		Temperature 102°.
4 5	24		6,150		Diff. 425 cells. Polynuclear, 69; lymphocytes, 30; eosinophiles, 1.

### HERPES TONSURANS.

Mark A. Brown¹ records this blood count: White cells, 10,700; of these, there were eosinophiles, 25.2 per cent; polynuclears, 45.6 per cent; lymphocytes, 29.2 per cent.

#### CHRONIC ECZEMA.

Thomas R. Brown<sup>2</sup> reports a case of chronic eczema, studied at the Johns Hopkins Hospital, in which three counts showed 22.6 per cent, 24 per cent, and 22.7 per cent. of eosinophiles.

Zappert (*loc. cit.*) notes a similar case with 8,600 leucocytes per cubic millimetre, 9.9 per cent of which were eosinophiles (843 absolute). Bettmann records 45 per cent eosinophiles in a similar case.

#### SCLERODERMA.

Two cases in Zappert's series showed:

I	eucocytes.	eosinophiles.				
1	16,690	9.4 (1:	,580	absolute)	)	
2	9,000	7.7 (	694	66	)	

Per cent

#### PSORIASIS.

One of Zappert's cases had 8,600 leucocytes, with 9.8 per cent of eosinophiles (850 absolute).

<sup>&</sup>lt;sup>1</sup> In Conn. Lancet-Clinic, December 22d, 1900.

<sup>&</sup>lt;sup>2</sup> Jour. of Exp. Med., vol. iii., p. 320.

### PEMPHIGUS.

# Zappert's three cases showed:

Cases.	Red cells.	White cells.	Per cent eosinophiles.
1	3,940,000	5,300 10,600 1,640	33.0 (1,750 absolute). 14.1 (1,500 absolute). 29.2 (4,800 absolute).

### LUPUS.

# Two cases (Zappert).

Cases.	Red cells.	White cells.	Per cent eosinophiles.
1		9,200	12.2 (1,126 absolute).
2		9,450	7.3 ( 696 absolute).

### CHAPTER XIV.

#### THE BLOOD IN INFANCY.

I. All the signs by which sickness is shown in the blood of adults are exaggerated in children. Their blood is apparently more sensitive to the action of any morbid influence. Causes leading to but slight anæmia or leucocytosis in the adult, produce grave anæmia and very marked leucocytosis in children. Into the reasons for this I shall not attempt to enter. The increased toxicity of their serum compared to that of adults, and the relatively recent establishment of the functions for producing and destroying blood have been suggested as explanation.

Comparatively slight hemorrhages, gastro-intestinal or respiratory disorders, which would not impoverish an adult's blood may produce considerable anæmia in a young child.

- II. All forms of anæmia in infancy are apt to be associated with enlarged spleen.
- III. I have already alluded to the polycythæmia and leucocytosis of the new-born, and the gradual fading out of these relative abnormalities as the child grows up. In judgments as to the presence or absence of leucocytosis in infancy, these physiological variations are too often lost sight of, especially as the proper leucocyte count for any given infant depends not simply on its age but on the backwardness or forwardness of its development. As with the fontanelles, the growth of the blood toward adult conditions may be retarded by congenital weakness (infantile atrophy, marasmus) or inherited disease (tuberculosis, syphilis) as well as by acquired sickness (rickets, cholera infantum).

Under the influence of any of these drawbacks a sick child's blood may be no further developed at three years than that of a healthy child of eighteen months.

IV. When we remember that in early infancy the leucocytes differ from those of adults not only in number but in that the lymphocytes are relatively more numerous ("lymphocytosis of infancy"), we shall understand that any influence like rickets or syphilis, which

retards development, will show lymphocytosis together with the increased leucocyte count. Qualitatively as well as quantitatively the blood reverts to a more infantile condition.

V. This shows itself not merely in the leucocytes but in the red corpuscles. During the first days after birth the infant's blood shows greater variations in size and shape than that of adults, as if the type were not yet quite fixed. The majority of authors also find a few normoblasts in the first few days of life. These are not invariably present, doubtless because in some children the blood at the time of birth is more developed than in others.

Under pathological conditions the red cells revert to this earlier type, and deformed or nucleated corpuscles are plentiful. This is more marked than in anemia of the same grade occurring in adults. An anemia that shows but thirty nucleated erythrocytes per cubic millimetre in an adult might show ten times that number in a child.

VI. As I said before, all blood changes are exaggerated in infancy. This includes such physiological changes as the digestion leucocytosis or that following cold bathing as well as pathological leucocytosis and anæmia, and changes in the degree of dilution or concentration of the blood seem to be similarly exaggerated, as is seen, e.g., in the physiological variations in the specific gravity of the serum (Hock and Schlesinger').

VII. The hæmoglobin, though relatively high at birth and for the first few weeks, is lower than that of adults during the rest of childhood. The high percentages of the earliest weeks are not due to a polycythæmia, but to a genuine increase of hæmoglobin in the individual cells (Schiff<sup>2</sup>), color indexes being often over 1.

It is indispensable, therefore, that we should know the age and degree of development of a child before we can draw accurate inferences from its blood. In many of the cases reported in literature we are unable to judge whether the blood condition is pathological or not, because the age of the child is not given. For example, v. Limbeck <sup>3</sup> notes a case of acute gastritis reported by Fischl <sup>4</sup> as having an unusually high percentage of lymphocytes (59.4 per cent). But this is physiological in the first days of life, and may have been so in this case, the age not being given.

<sup>&</sup>lt;sup>1</sup> Hock and Schlesinger: Centralbl. f. klin. Med., 1891.

<sup>&</sup>lt;sup>2</sup> Schiff: Zeit. f. Heilk., vol. xi., 1890.

<sup>&</sup>lt;sup>3</sup> v. Limbeck: *loc. cit.*, p. 373.

<sup>&</sup>lt;sup>4</sup> Fischl: Zeit. f. Heilkunde, 1892.

Observations of this sort should always represent a comparison between the conditions present *before* and *during* the sickness in question.

Bearing these general considerations in mind, we shall be better able to find our way among the complications and perplexities of the blood conditions in infancy.

#### THE ANÆMIAS OF INFANCY.

As above mentioned, anæmic infants are apt to have enlarged spleens. This may be due either to the anæmia or to some disease accompanying or underlying the anæmia (e.g., rickets, syphilis). It seems more probable that the hypertrophy is not directly or exclusively dependent on the anæmia, inasmuch as similar blood changes are found without splenic enlargement. By far the greater number of reported cases of severe infantile anæmia are accompanied or caused by such diseases as rickets and hereditary syphilis, both of which may cause splenic hyperplasia even when no anæmia is present. It seems probable that the anæmia and the enlargement of the spleen are alike symptomatic of an underlying disorder.

- 1. Some writers (e.g., Luzet¹) divide the anæmias of infancy into two classes: those with splenic enlargement and those without it. Luzet considers that the former class is severer than the latter and more apt to show large numbers of nucleated red corpuscles than those with normal-sized spleens. This classification, however, does not always hold. We may have very severe anæmia without splenic enlargement and splenic enlargement with slight anæmia, and the presence or absence of numerous nucleated red corpuscles is governed by conditions other than the size of the spleen.
- 2. Another classification of children's anæmias was proposed in 1892 by Monti and Berggrün ("Die chronische Anämie im Kindesalter," Leipzig, 1892). They divided the cases into the *mild* and the *grave*, each group being subdivided into those with leucocytosis and those without it.

They rightly discard the term "splenic anæmia," corresponding as it does to no single set of blood changes. The above classificative: Diss., Paris, 1891.

tion puts pernicious anæmia, leukæmia, and anæmia infantum pseudoleukæmica (v. Jaksch) in a different category.

- (a) Mild cases of secondary anæmia show no deformities in the shape or size of the red cells. The color index may or may not be low. The cases with leucocytosis are much more numerous than those without it and more apt to have a low color index; in other words, the loss of corpuscle substance is greater and the cases are approaching the imaginary boundary between "mild" and "grave."
- (b) The grave cases have poikilocytosis, and of course a greater reduction of corpuscle substance.

"Chlorotic" conditions, and most but not all those with enlarged spleen, come under this heading; also most of those due to hereditary syphilis, prolonged diarrhea, and rickets.

In 1894 Monti <sup>1</sup> gave the following classified lists of the commonest antecedents of secondary anæmia in infancy:

He points out that cases with leucocytosis are usually graver than those without it and may develop into pernicious anæmia; also that the presence of leucocytosis does not point to malignant disease, suppuration, or any of the causes which usually account for it in adults.

Grave cases with leucocytosis in infants under twelve months are apt to develop into the anæmia infantum pseudoleukæmica, or into true leukæmia or pernicious anæmia.

On the whole, the division of Monti and Berggrün seems much better than that according to the particular causes, e.g., "rachitic anæmia," "syphilitic anæmia," etc., for there is no particular set

of blood changes that follows rickets, syphilis, or any other disease. In connection with various diseases of infancy, and particularly with those last named, we may have anæmia of any grade of severity, from that reducing the red cells to 4,000,000 down to cases with only 500,000 red cells per cubic millimetre or even less. The worse the case is the more likely is it to be accompanied by leucocytosis and the more numerous will be the nucleated red corpuscles, always more numerous here than in anæmia of adults.

In *syphilis*, hereditary or acquired, the red cells may fall below 1,000,000 and the leucocytes may rise as high as 58,000 (Loos). The hæmoglobin may be proportionally diminished, or may be even lower than the percentage of red cells, so that a "chlorotic" condition obtains.

Such cases have been called *chlorosis*, but it seems better to confine this term to anæmia of unknown origin and favorable course occurring in women soon after puberty, since obviously secondary cases may have similar blood.

*Rickets* in a case observed by v. Jaksch caused a fall of the red cells to 750,000, and Luzet counted 1,590,000 in a similar case. The hæmoglobin is usually low, but Hock and Schlesinger found 60 per cent with 2,300,000 red cells, a color index of 1.2 + ...

Leucocytosis may occur even when no anæmia is present. Hock and Schlesinger found 45,000 leucocytes in a rachitic child of sixteen months, sound in other respects and not anæmic. Acute gastritis causes at first only leucocytosis (with increased percentage of lymphocytes). If it becomes chronic the reduction of red cells is severe. Hayem found only 685,000 red cells per cubic millimetre in an infant of two months, though recovery eventually took place.

In *tuberculosis* of the lungs and peritoneum in a child of seven, Monti and Berggrün counted 3,230,000 red and 17,200 white cells with 52 per cent of hæmoglobin.

#### Qualitative Changes.

The exaggeration characteristic of all blood changes in infancy extends to the presence of nucleated red corpuscles, which in all forms of severe anæmia are very numerous. What has been described above (page 91) as the typical megaloblast, a large palestained nucleus in a very large cell (see Plate IV.), is relatively rare in infancy. The nuclei are almost always deeply stained whatever their size, and apt to be small. Dividing nuclei are very com-

mon, both by karyolysis and karyokinesis. These changes are most often found in the anæmias of the severest type and those which resemble leukæmia (see below, page 456), but may occur in any marked secondary anæmia. Polychromatophilic and "degenerative" changes are very common in severe cases.

The increased leucocyte count, so frequently found, is often made up of a majority of lymphocytes. This change, as above said, is not characteristic of rickets, syphilis, or any other cause of anæmia, but it is to be regarded as a mark of the arrest of development or reversion to an earlier type of tissues brought about by various diseases in early infancy. Sometimes the large lymphocytes and sometimes the small are in excess.

A further qualitative change already alluded to (see above, page 118) is the occurrence of *myelocytes*. We have seen that small percentages of these cells are not uncommonly seen in the anæmias of adults. Now this, like all other blood changes, is exaggerated in infancy. Myelocytes are more apt to appear and in greater numbers. Their presence is not characteristic of any one disease, but they are commonest in the severer types of secondary anæmia, such as those following syphilis and rickets. Their significance is about the same as that of normoblasts. At times, however, they are so numerous as to make us hesitate somewhat before we exclude splenic-myelogenous leukæmia.

This brings us naturally to the discussion of the difficulty of distinguishing the different blood diseases in infancy, which naturally centres in the question of the existence and nature of the so-called

#### "ANÆMIA INFANTUM PSEUDOLEUKÆMICA."

Von Jaksch's description of this disease (which he was the first to recognize) includes the following elements:

- 1. Grave anæmia—e.g., 820,000 red cells per cubic millimetre in one case.
- 2. Extensive leucocytosis—e.g., 54,660 white cells per cubic millimetre, in the same case.
- 3. Great variations in the form, size, and staining of the white cells.
  - 4. Deformed, degenerated, and nucleated red cells.

Von Jaksch admits that none of these blood changes is charac-

<sup>1</sup> Von Jaksch: Wien. klin. Woch., 1889, Nos. 22, 23.

teristic of the disease, but thinks that its title to the position of a distinct and separate disease rests upon *clinical* data, the more important of which are: (1) A great enlargement of the spleen without any such accompanying enlargement of the *liver* as is usually found in leukæmia (the lymph glands are sometimes enlarged). (2) A relatively good prognosis. (3) Post mortem we find no positive evidence of leukæmia.

This description was given by v. Jaksch in 1889. He stated the relation of white to red corpuscles as 1:12, 1:17, and 1:20 in the cases seen by him. Later he reported three cases in one of which the white cells numbered 114,150, and the red 1,380,000. The differential counts are not carefully given.

Almost at the same time Hayem<sup>2</sup> reported a similar case, and noted the abundance of nucleated red corpuscles many of which were undergoing mitosis. This was verified by Luzet<sup>3</sup> in May, 1891 (Arch. gén. de Méd.), who reported two cases. His description of the disease differs considerably from that of v. Jaksch. He finds no greater difference between liver and spleen than often exists in true leukæmia. The course of the disease, though sometimes chronic, usually ends in death. The leucocytosis in Luzet's cases was less marked than in those of v. Jaksch and not greater than that occurring in many anæmias of children. He dwells particularly on the large number of nucleated red cells, and the frequency of mitosis, and considers this the most important diagnostic point.

Although Luzet continues to use the name suggested by v. Jaksch, he describes the disease so differently that it is difficult to see why the same title should be given to it. He agrees with v. Jaksch in thinking that it is not simply a severe secondary anæmia due to syphilis, rickets, tuberculosis, or infectious disease.

Somewhat similar cases had already been described by various Italian writers (e.g., Fede) under the title of "Infective Splenic Anæmia of Infants."

Among others who have written on the subject are Baginsky, <sup>4</sup> Senator, <sup>5</sup> Fischl, <sup>6</sup> Andeoud, <sup>7</sup> Monti and Berggrün, <sup>8</sup> Felsenthal, <sup>9</sup>

<sup>1</sup> Von Jaksch: Wien, klin, Woch., 1889, Nos. 22, 23.

<sup>&</sup>lt;sup>2</sup> Hayem: Gaz. des Hôpitaux, 1889, No. 30.

<sup>&</sup>lt;sup>3</sup> Luzet: Diss., Paris, 1891.

<sup>&</sup>lt;sup>4</sup> Baginsky: Arch. f. Kinderheilk., 1892, vol. xiii.

<sup>&</sup>lt;sup>7</sup> Andeoud: Rev. méd. de la Suisse rom., 1894, p. 507.

<sup>&</sup>lt;sup>8</sup> Monti and Berggrün: loc. cit. <sup>9</sup> Felsenthal: loc. cit.

Raudnitz, Epstein, Alt and Weiss, Hock and Schlesinger, Croeq, and Rotch.

The majority of these writers report very little as to the differential counts of white corpuscles. An increased percentage of the polymorphonuclear forms is mentioned by many, but Rotch in a case with 1,311,250 red cells and 116,500 white cells found only 16 per cent of the polymorphonuclear variety with 46 per cent of small lymphocytes, 34 per cent of large lymphocytes, and 4 per cent cosinophiles. A second case had only 14 per cent of polymorphonuclear cells and 84 per cent of lymphocytes (large and small).

Von Jaksch noted the lack of any relative increase of eosinophiles, supposing this to be a means of distinguishing his cases from true leukæmia. Luzet, on the other hand, found eosinophiles numerous. (This of course has no weight for or against leukæmia.)

Klein  $(loc.\ cit.)$  noted the occurrence of myelocytes in small number.

The discrepancy of these different reports is suggestive.

The chief importance of the heterogeneous group of cases which have received the name of *anæmia infuntum pseudoleukæmica* seems to me to be as a proof of the difficulty of distinguishing the various blood diseases in infancy.

Among the cases reported under this name are some which might be any one of the following list: Pernicious anæmia, secondary anæmia with leucocytosis, Hodgkin's disease, lymphatic leukæmia, and probably splenic-myelogenous leukæmia.

(a) Most of the few reported cases of pernicious anæmia in infancy have shown moderate leucocytosis (as compared with adult blood), a fact which deprives us of one of the means of distinguishing the disease from secondary anæmia. The reports as to nucleated corpuscles very rarely separate normoblasts from megaloblasts, and we have no way, therefore, of being sure on this important point. The high color index and large diameter of the red cells are occasionally seen in other anæmias of infancy and are not always present in pernicious cases. The great fatality of all kinds of anæmia in

<sup>&</sup>lt;sup>1</sup> Raudnitz: Prag. med. Woch., 1894, p. 6.

 $<sup>^2\,\</sup>mathrm{Epstein}\colon\,\mathrm{Prag.}$ med. Woch., 1894, p. 6.

<sup>&</sup>lt;sup>3</sup> Alt and Weiss: Centralb. f. med. Wissenschaft., 1892.

<sup>&</sup>lt;sup>4</sup> Hock and Schlesinger: loc. cit.

 $<sup>^5\,\</sup>mathrm{Crocq}\colon$  "Étude sur l'Adénie," etc., Brussels, 1819 (Lamartin).

<sup>&</sup>lt;sup>6</sup> Rotch: Pædiatrics, 1895, p. 361.

infancy prevents our calling a case *pernicious* because of a fatal termination. Enlargements of the liver and spleen occur in many cases of each type of infantile anæmia, and occasionally in pernicious anæmia of adults. They do not, therefore, exclude pernicious anæmia in infancy.

Bearing these facts in mind, it is evident that some of Luzet's cases of "anæmia infantum pseudoleukæmica" may have been pernicious anæmia. Von Jaksch's own cases may have been either (a) Hodgkin's disease with leucocytosis, (b) grave secondary anæmia with leucocytosis (Monti and Berggrün), or (c) leukæmia.

- (a) Hodgkin's disease, which v. Limbeck finds to be very common in infancy, may affect the liver and spleen and not the external lymph glands, and may be accompanied by anæmia and leucocytosis such as v. Jaksch describes. Epstein considers that this is the case, and denies the existence of any such disease as the anæmia infantum pseudoleukæmica.
- (b) As any anæmia secondary to rickets or syphilis may have enlarged spleen and liver and marked leucocytosis, we cannot tell from v. Jaksch's description that we are not dealing in his cases with secondary anæmia.
- (c) Since v. Jaksch does not give any accurate differential count of the leucocytes, there may have been large numbers of myelocytes in his cases for all we know, or an overwhelming percentage of lymphocytes, i.e., either type of leukæmia.

One of the cases reported by Rotch as "anæmia infantum pseudoleukæmica" had 80 per cent of lymphocytes in a leucocyte count of 116,500, the ratio of white to red cells being 1:11, and the nucleated corpuscles abundant. The external lymph glands as well as the liver and spleen were enlarged. How such a case is to be distinguished from lymphatic leukæmia without autopsy I cannot see. Large numbers of nucleated corpuscles with mitoses (present in this case) are to be found in any anæmia of infancy in which the red cells, as in this case, have sunk as low as 1,311,500, and therefore do not exclude leukæmia.

Von Jaksch protests that his cases are not secondary to rickets or any other disease, but Fischl in a careful study of all the published cases finds that, out of a total of eighteen cases, sixteen had severe rickets and two hereditary syphilis.

The writings of Raudnitz, Ebstein, Felsenthal, Fischl, and v.

<sup>1</sup> Fischl: Zeit, f. Heilkunde, 1892.

Limbeck, which deny the separate existence of the anæmia infantum pseudoleukæmica, are convincing to me, and are reinforced by the few cases of bad anæmia in children which I have seen. We must distribute the cases of anæmia with leucocytosis and large spleen under pernicious anæmia, secondary anæmia, and leukæmia.

But our problem is not yet nearly solved. All we have gained is the belief that v. Jaksch's new disease does not help us to classify these doubtful cases. The difficulty is still very great. The following cases reported by Dr. Vickery in the Medical News for December, 1897, illustrate this:

Case I.—A male child of sixteen months with symptoms of grave anæmia, greatly enlarged spleen and slightly enlarged liver, showed the following figures: Red cells, 2,500,000; white cells, 22,000. Differential count of 500 cells showed: Lymphocytes, 53.8 per cent (46.2 of the smaller type); polymorphonuclear cells, 29.4 per cent; eosinophiles, 6.2 per cent; myelocytes, 10 per cent.

While counting these, 147 nucleated red corpuscles were seen, of which 21 were normoblasts, 50 megaloblasts, and 47 microblasts;

6 showed mitosis in their nuclei.

The child died shortly after without any complication or intercurrent disease. No autopsy. No evidence of rickets or syphilis

or other previous disease.

Case II.—Young infant with enlarged external lymph glands and very large spleen. July 14th, 1897—Red cells, 4,300,000; white cells, 31,000; hæmoglobin, 60 per cent; polymorphonuclear neutrophiles, 57.5 per cent; small lymphocytes, 26 per cent; large lymphocytes, 15 per cent; eosinophiles, 0.5 per cent; myelocytes, 1 per cent.

One or two nucleated red corpuscles in every field. Out of 100 of them 89 were large and 11 small. Many showed mitosis. Polychromatophilic forms numerous. July 19th—Seventeen megaloblasts seen while counting 1,000 white cells. Blood is otherwise

about the same. The case was lost sight of and not traced.

Now I see no reason for supposing these cases to represent a new type of disease, and yet I cannot feel perfectly safe in classifying them as primary anæmia, secondary anæmia, or leukæmia.

- (a) Primary or pernicious anæmia should have a lower count of red cells. The percentage of myelocytes in the first case (10 per cent) is higher than in any other case of pernicious anæmia on record, though in one adult case with autopsy I found 9.2 per cent with a leucocytosis of 12,500, or 1,150 myelocytes per cubic millimetre, against 2,200 per cubic millimetre in this case.
  - (b) It is hard to call an anemia secondary which kills with no

complications and when there is no evidence of any disease to which it can be secondary.

(c) For splenic myelogenous leukæmia the total leucocyte count and the percentage of myelocytes are very small in either case. Still the leucocyte count may drop very low in leukæmia even without any inflammatory complication. Such a case is reported by Osler, in which the leucocytes fell to 7,500, of which only 300, or four per cent, were myelocytes.

Hayem (*loc. cit.*, page 864) in a ten-months old child counted 2,712,500 red and 33,000 white cells, almost the same figures as in the case just quoted. [Hayem unfortunately gives no differential count, but apparently considers the case leukæmic because of the enormous number of nucleated red cells, many with mitoses.]

Morse's case of leukæmia in infancy had 2,900,000 red and 48,000 white cells. Twenty-one and four-tenths per cent of the leucocytes, or about 10,000, were myelocytes. The same abundance of nucleated red cells (some with mitoses) were here present as in Hayem's case, so that there is evidently nothing peculiar in their presence in the disease described by v. Jaksch, as Luzet supposed.

These cases show that leukæmia may at certain periods present just such a blood picture as was present in the above-quoted case, and that the number of leucocytes in the leukæmia of infants may be no greater than that in any anæmia with the leucocytosis so common in children.

It seems to me the most natural conclusion to be deduced from these facts is that we meet with cases in infancy which are apparently intermediate between leukæmia and pernicious anæmia. I have pointed out elsewhere that there are many points of resemblance between the two diseases. The case of leukæmia reported by Osler showed at one period—the period of remission—a fall in the number of leucocytes and in the percentage of myelocytes till the blood was practically that of pernicious anæmia.

Dr. Rotch's case (above quoted) is another in which the diagnosis seems to lie somewhere intermediate between the two diseases, anæmia and leukæmia.

The case which I have quoted above seems to me on the whole nearer to the type of pernicious anæmia than of leukæmia, and Dr. Rotch's nearer to the latter than to the former; but each is really intermediate, so far as the blood goes, between the two diseases. I

have no intention of suggesting that the organic lesions in these cases are intermediate between leukæmia and pernicious anæmia. It is simply the blood that is so.

Engel's case, reported in Virchow's Archiv, vol. 135, suggests the same thing. He calls the case one of "pseudo-pernicious anw-mia." Myelocytes were abundant.

#### Polymorphous Condition.

This illustrates that "polymorphous" condition of the blood which v. Jaksch supposed to be characteristic of the anæmia infantum pseudoleukæmica. The same thing was very marked in all the bad cases of anæmia which I have seen, including the case above mentioned, and a case of true leukæmia in a girl of eight. The impression one gets from the field of a stained specimen is that no two white corpuscles are alike. Every species is subdivided into several sub-varieties and all stages of degeneration are to be seen in each variety. But this is characteristic of any very severe infantile anæmia and not of any single type.

#### LEUKÆMIA.

In Morse's careful article of August, 1894 (Boston Med. and Surg. Journal), twenty cases of leukæmia in infancy are collected. As he rightly says, probably most of these cases were not genuine. Only one of them includes a differential count, and this is in a lymphatic case. Morse's is the only one of the splenic-myelogenous type on record in which the diagnosis is made reasonably certain by a color analysis. Fischl in 1892 said that there was no case on record with a differential count.

A case was seen in 1890 by Dr. F. C. Shattuck, which was apparently acute, the symptoms appearing only six weeks before death. Cover-glass preparations examined by W. S. Thayer showed a ratio of about 1 white to 20 red cells. The differential count showed: Small lymphocytes, 97.9 per cent; large lymphocytes, .7 per cent; polynuclear cells, 1.4 per cent; eosinophiles, .08 per cent.

The other case reported by Morse has been mentioned above. Charon and Giratea<sup>2</sup> have recently reported a case in a child of

 $<sup>^{\</sup>rm f}$  Reported by Thayer in the Boston Medical and Surgical Journal, 1893, vol. cxxviii., p. 183.

<sup>&</sup>lt;sup>2</sup> Bull. d. Soc. Roy. d. Sciences Méd., etc., Bruxelles, 1897, No. 7.

eight with 880,000 red cells, 305,000 white cells, and 39 per cent of hæmoglobin. It was apparently of the myelocyte type. E. Müller thinks that there are about five other (German) cases on record, all of acute leukæmia and all with a similar blood count, though in some the large lymphocytes (without neutrophilic granules) have been described as "myelocytes."

Müller' has lately reported with great care three cases of leukæmia, all of them in boys four years old—all apparently acute, all of the gastro-intestinal type—i.e., the glands and follicles throughout the whole length of the alimentary tract being the chief seats of infiltration, though the liver and spleen were also enlarged. The counts were as follows:

		Cas	SE I.			
	April 30th.	May 1st.	May 2d.	May 3d.	CASE II.	Case III.
Red cells	1,508,000 109,500 40%		1,362,000 46,000	1,232,000 6,800 Death.	2,290,000 206,000 25%	1,308,000 42 <b>0</b> ,000
Polymorphonuc le a r neutrophiles Small lymphocytes Large lymphocytes Eosinophiles		2% -10 μ dian 13%		Many. Few. Few. Many.	1% 15% 84%	2. 97.3 .01
Normoblasts			ew. ew.		Two normoblasts seen in counting 1,135 leu-cocytes.	

<sup>&</sup>lt;sup>1</sup> Jahrbuch für Kinderheilk., 1896, vol. xliii.

<sup>&</sup>lt;sup>2</sup> All with large pale nuclei.

# PART VII. EXAMINATION OF THE SERUM.

#### CHAPTER XV.

#### THE CLUMP REACTION.

GENERAL DESCRIPTION.

Although this phenomenon is to be obtained in various infections, natural as well as experimental, and with various body fluids, I shall describe as a typical case of it the reaction which may take place when the serum of a patient ill with typhoid fever is added in certain proportions (vide infra) to a young bouillon culture of well-certified and virulent typhoid bacilli. In a drop of such a mixture, examined between slide and cover-glass' with a magnification of 300 diameters or more, we notice, at once or within thirty minutes, a marked slowing of the progressive movements of the bacilli or an unequal distribution of them in the different parts of the preparation. Whichever of these changes occurs first, the slowing of locomotion or the tendency to grouping, the other soon follows, and then both processes go on together, as admirably described by Biggs and Park:<sup>2</sup>

"Some of the bacilli soon cease all progressive movement, and it will be seen that they are gathering together in small groups of two or more, the individual bacilli being still somewhat separated from each other. Gradually they close up the spaces between them, and clumps are formed. According to the completeness of the reaction, either all the bacilli may finally become clumped and immobilized or only a small portion of them, the rest remaining

<sup>&</sup>lt;sup>1</sup> Hanging-drop preparations are often recommended, but a simple slide and cover-glass are as good for the purposes of this reaction.

<sup>&</sup>lt;sup>2</sup> American Journal of the Medical Sciences, March, 1897.

freely motile, and even those clumped may appear to be struggling for freedom. With blood containing a large amount of the agglutinating substances all gradations in the intensity of the reaction may be observed, from those shown in a marked and immediate reaction to those appearing in a late and indefinite one, by simply

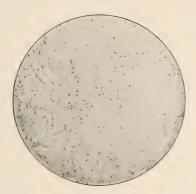


Fig. 49.—Pure Culture.

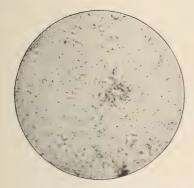


Fig. 50.—Partial Reaction.

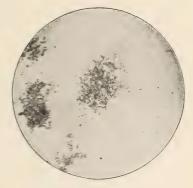


Fig. 51.—Typical Clumping.

varying the proportion of blood added to the culture fluid" (see Figs. 49, 50, and 51).

The process may go on gradually and be much more distinct at the end of half an hour.

The groups or clumps above described constitute the important part of the reaction for diagnostic purposes. Of the loss of motility more will be said later. TECHNIQUE OF THE CLUMP REACTION IN TYPHOID FEVER.

Our account of the methods of obtaining the clump reaction may be divided into the following parts:

- 1. The body fluids to be used and the methods of obtaining them.
  - 2. The cultures.
  - 3. Dilution and the time limit.

#### 1. The Body Fluids to be Used.

Experiments have proved that the reaction can be obtained with the following fluids:

- (a) The whole blood, fluid or dried.
- (b) The plasma and serum, fluid or dried.
- (c) Also blister fluid, the fluid contents of normal serous cavities, breast milk, pus, tears, and other body fluids.

Of all these fluids, the blood, or the serum, fresh or dried blisters are the only ones used in clinical work.

#### 1. Use of the Whole Blood-Fluid.

The advantages of this method are (a) its quickness, and (b) the small amount of blood (one drop) sufficient for the test.

I have used this method in most of my cases and always found it satisfactory and convenient.

Procedure.—Suck up some water with a medicine-dropper and expel ten drops of it into a watch-glass. Then empty and dry the dropper, draw up from the watch-glass the ten drops just expelled, and mark with a file on the side of the dropper the point up to which the ten-drop column extends. Mark also the point to which one drop (expelled and then sucked up again as before) will rise.

Ten drops of the bouillon culture of the bacilli to be used are then expelled into each of several small test-tubes, and one of these tubes is carried to the bedside. After pricking the ear as if for blood examination (see page 7), put the end of the medicine-dropper into the blood drop, and carefully draw back the rubber bulb (which has been previously pushed down over the glass part of the dropper) until the blood rises to the mark for one drop. Wipe from the outside of the dropper any blood that may adhere there

 $<sup>^1\,\</sup>mathrm{Squeezing}$  and milking the ear are of no harm in this procedure and enable us to get on with a trifling and painless puncture.

and then expel the drop into one of the little test-tubes containing the ten drops of bouillon culture. In this way blood can be taken for examination from a dozen patients in as many minutes.

#### 2. Whole Blood-Dried.

The advantages of the method are (a) the ease and quickness with which the blood can be obtained, (b) the convenience for transportation by mail, and (c) that it does not deteriorate or become contaminated by bacterial growth, as specimens of fluid blood or serum are so apt to do. Its clumping power is fully equal to that of the serum in most cases.

Procedure.—The blood should be dried either upon a glass slide or on a piece of glazed paper or card. Any absorbent substance is less available. Glass is easier to sterilize than paper. Several large drops should be placed in different parts of the glass or paper and thoroughly dried.

If paper has been used, we cut out the dried blood drop with a pair of scissors, keeping close to the blood all round, and drop it into a test-tube containing one or two drops of water, in which with some sharp-pointed instrument we mix the dried blood, freeing it as well as possible from the paper.

To the liquid so obtained add eight or nine drops of the bouillon culture of bacilli and proceed in the ordinary way. Or we may drop the fragment of paper holding the blood directly into ten drops of bouillon culture—using the bouillon itself to soak off the blood from the paper.<sup>2</sup>

#### The Fluid Serum.

The ear is pricked in the ordinary way and about twenty drops are forced out by strong squeezing. The blood is received in a small (preferably two-inch) test-tube.

The blood when collected may be at once centrifugalized, and the plasma used for the test, or we may wait till clotting occurs

<sup>1</sup> Widal and Delépine think the fluid serum is slightly more powerful than the dried blood. Johnson admits that in one-tenth of the cases the serum is the more powerful. I have obtained reactions with the dried blood in only seven-eighths of the cases in which I got them with the fluid serum.

<sup>2</sup> Some observers gather the blood on a bit of tinfoil and later crack it off, and after weighing it can make exact dilutions. Or we may soak blood into bits of filter paper of standard size and porosity and thus acquire a known amount as a basis for exact dilutions.

and use the serum. When blood is collected in test-tubes, it is convenient to free the edges of the clot from the tube all round with some sharp instrument, so that the serum may not be pinned down underneath the clot, as it often is. If this is done, a drop of serum can be had within two or three minutes, and is then mixed with ten drops of bouillon culture, as above described, and examined at once between slide and cover-glass.

(Dried serum can be used in the same way as dried blood, but has no special advantages and has not been frequently employed by any observer.)

#### 2. THE CULTURES OF TYPHOID BACILLI TO BE USED.

- 1. The stock cultures grow best on agar at room temperature.
- 2. Ordinary peptone bouillon, free from sediment, is the best medium for the test culture. It should be just on the verge of litmus acidity, giving no blue to the red paper and requiring 3.5 per cent of normal alkali to render it neutral to phenolphthalein.
- 3. The cultures should be *young*—that is, the transplantation to bouillon should have taken place not more than from twelve to twenty-four hours before the culture is used.
- 4. The virulence and motility of the culture are very important. Most observers agree that the more virulent the culture the more readily and characteristically it is clumped by typhoid serum. Biggs and Park noticed that one culture of peculiarly great virulence recently received from Pfeiffer of Berlin worked much better in their cases than any other of the cultures used.

Cultures fresh from an autopsy usually show furious motility, the bacilli darting about like a swarm of insects, but after repeated transplantations and long sojourn in the thermostat a good deal of this motility is gradually lost. Cultures kept at room temperature preserve their motility for much longer periods.

For those who have no opportunity to test the virulence of organisms on animals, the motility is the best guide to virulence, and the rule should be: Among the available cultures select that having the most rapid motility.

- 4. Certain cultures contain small clumps of bacilli before any serum has been added to them. This is a very important point and has doubtless misled many. In consequence of this possibility every culture must be examined each time that a test is made.
  - 5. It is hardly necessary to say that the cultures used must have

been submitted to all the regular tests for the recognition of the typhoid bacillus, and that the greatest care must be used to avoid their contamination.

## The Use of Suspensions or Emulsions of the Bacilli instead of Cultures.

A few observers—particularly Durham and Grüber—have preferred to use a mixture of small bits of solid agar culture and bouillon instead of bouillon cultures. The majority of writers prefer cultures.

#### The Use of Attenuated Cultures.

Johnson finds that with his methods of technique (dried blood and no definite dilution) pseudo-reactions were not uncommon with the blood of healthy people.

He avoids this by using attenuated cultures -i.e., old stock agar cultures kept at room temperature and not transplanted more than once a month, from which he planted his bouillon cultures. This gives a bacillus of reduced virulence and slow, gliding motion, which is clumped far less readily than the virulent varieties. Bouillon cultures of this kind from twelve to twenty-four hours old he found to react in fifteen minutes with all typhoid sera and not with other sera even after forty-eight hours' waiting.

#### 3. DILUTION AND THE TIME LIMIT.

#### I. Dilution.

I have mentioned without explanation in various parts of this chapter that the blood serum or other fluids used must be diluted with at least ten times their volume of bouillon culture before any observation is made as to their action on the bacilli of typhoid fever.

The reasons for this dilution and for the proportions 1:10 are the following:

It has been found, as mentioned above, that the mere formation of clumps in bouillon cultures of Eberth's bacilli is not a power exclusively possessed by typhoid serum. The serum of persons suffering from other diseases and even of healthy persons will form clumps exactly like those formed by typhoid bacilli, provided it is not diluted. The only known peculiarity of the typhoid serum is that its clumping power is greater than that of other diseases, and

persists in spite of dilution, while the sera of diseases other than typhoid lose their power to clump typhoid bacilli when diluted ten times or more.

#### II. Time Limit.

But even this statement must be further limited. The sera of various other diseases, and of healthy persons, will sometimes clump typhoid bacilli even in a 1:10 dilution, provided we give them time enough. We must therefore limit the period within which a serum must "come up to the scratch" and do its work, if it is to be considered a typhoid serum.

Following Grüber and Durham, a time limit of one-half hour has been adopted by Grünbaum, Block, Haedke, Park, and others.

All that these more or less arbitrary figures stand for is this: that hitherto no one has reported any considerable number of cases in which the serum of any disease or of healthy persons has clumped typhoid bacilli within one-half hour, when diluted 1:10 and used with unimpeachable technique.

#### The Microscopical Examination.

An artificial light is preferable. The use of hanging-drop preparations is unnecessary, as a simple slide with cover-glass is satisfactory. A hanging-drop cell may be extemporized by cementing with marine glue a small brass curtain ring to a slide, and inverting the cover-glass within it, as advised by Stokes.

I have collected over 3,000 cases of supposed typhoid fever in which the clump reaction was tested as above described either with the fluid or dried blood. Of these, 95 per cent showed a serum reaction at some time in their course; 2,500 odd controls showed about 2 per cent of positive results in cases other than typhoid. Altogether then about 5,500 cases have been tested. If we leave out the reports of those whose experience covers less than 100 cases, we have left 4,339 cases observed by 18 physicians in which the percentage of error is 2 per cent only.

How early does the reaction appear?

Few of the many observers who have written on this point have discussed how the beginning of the disease is settled and what they mean, e.g., by the "fifth day of the disease." It might be dated from the first day of malaise and indisposition, from the nose-bleed or the beginning of headache, or from the time of going to bed.

Allowing for such serious uncertainties as this, we find that while the majority of observers record the sixth to eighth day as the earliest on which the reaction appears, there are quite a number of cases mentioned in which it was seen on the fourth or fifth day; a few record reactions present on the third day, and two or three on the second day.

How late in the disease does the reaction last? The majority of observations agree that in mild cases the reaction may die out even before the end of the fever. On the other hand, the reaction usually lasts several months, and Widal found it still present after one year in 3 out of 22 cases in which he tried it. These 3 subjects had had very severe cases of typhoid three, seven, and nine years previously. It has been reported present twenty and even thirty years after the fever.

The reaction almost always persists in relapses, even to a second or third relapse, and occasionally it is present only in relapse and not in the original attack at all. Biggs and Park record a case in which the diagnosis was proved during the original attack by puncture of the spleen, which showed a pure culture of Eberth's bacilli, yet no serum reaction was present until the second day of the relapse. I have observed several similar cases, and quite frequently not found the reaction until convalescence. The failure to follow up such cases as these accounts for many negative reports.

#### The Intensity of the Reaction.

Widal and Sicard record clumping with a dilution of 1:12,000 and 1:1,800 and consider that in the active stages of the disease a dilution of 1:60 or 1:80 does not usually present the reaction, while in convalescence the power of the serum falls off gradually and is not always present even at 1:10.

Biggs and Park find one-half their typhoid cases furnish serum with the power to clump in 1:40 dilution by the end of the first week, and have occasionally noted the reaction even with a dilution of 1:200.

#### Control Cases.

Out of over three thousand cases of various diseases not typhoid, not over a dozen have been proved to clump typhoid bacilli with proper technique. It is quite possible that further improvements in technique may enable us to prevent even this very small error.

30

# Summary of Clinical Evidence on the Sero-Diagnosis of Typhoid Fever.

The blood of over ninety-five per cent of all cases of typhoid shows a clumping power in some part of their course, but in at least half the cases this does not appear until the second week of the disease, while in a small number of cases it first appears in relapse or convalescence. The clumping power may disappear before the defervescence and may be present only eight days in all; as a rule it persists from the sixth or eighth day until convalescence is established.

In diseases other than typhoid a clump reaction is very rarely to be obtained, provided a dilution of at least 1:10 is used with a time limit of one-half hour. There is no one disease in which clumping is especially apt to occur.

Clinically the reaction is of considerable value, especially when the diagnosis is in doubt after the first week of the disease.

#### SERO-DIAGNOSIS OF DISEASES OTHER THAN TYPHOID.

#### 1. Cholera.

Grüber and Durham first showed that human cholera serum would clump cholera vibrios, following the researches of Pfeiffer in vivo by demonstrating a similar reaction in vitro.

Achard and Bensaude have applied this to the actual diagnosis of cholera in man with considerable success. In fourteen cases, thirteen clumped readily; two of these were on the first day of the disease. Thirty control cases were negative. The presence of the pellicle renders it unsafe to use bouillon cultures except such as have no pellicle, for bits of it are much like true clumps. Suspensions of twenty-hour gelatin cultures are more convenient. The dilution and time limit are the same as in typhoid. Some cases will react even in 1:120 dilution. The reaction can be performed with dried blood and persists into convalescence (seven months or more).

#### 2. Malta Fever.

Wright and Smith tested the serum of 15 cases of Malta fever with the *micrococcus melitensis* of Bruce, and found a strong clump reaction to occur (1:50 in most cases). On the typhoid bacillus the serum of these cases had no action. Sixteen cases of typhoid

showed no reaction with Bruce's organism. The evidence in favor of this organism as the cause of Malta fever is strengthened by these facts. Wright's observations have been confirmed by Neusser and others in this country.

Curry in a very recent number of the Boston Medical and Surgical Journal reports eighteen cases with clumping.

#### 3. The Bubonic Plague.

Zabolotny' studied forty cases at Bombay in April, 1897, and found the reaction absent in the first week, present in 1:10 dilution in the second week, and in 1:50 dilution in the third or fourth week. He noted that the action of the infected serum seemed to deprive the bacilli of their capsules. In an editorial in the Arch. Russes de Pathologie, May 31st, 1897, it is stated that the reaction increases in intensity until the fourth week of the disease and then declines; also that it is most marked in the severest cases. Feindel (loc. cit.) states that in the acute pneumonic cases the reaction is absent.

<sup>1</sup> Deut. med. Woch., 1897, p. 392.



### APPENDIX A.

#### NEUSSER'S PERINUCLEAR BASOPHILIC GRANULES.

Using the following modification of Ehrlich's tricolor mixture, Neusser¹ believes that he can bring out certain characteristics in the leucocytes of value in diagnosis and prognosis.

Saturated aqueous solution of	Acid fuchsin Orange G Methyl green	50 c.c. 70 " 80 "
Distilled water		
Absolute alcohol		80 "
Glycerin		20 "

Cover slips stained with this mixture show in certain diseases (e.g., gout, leukæmia) a grouping of dark blue-stained granules around the nuclei of the mononuclear leucocytes and over and around the nuclei of polymorphonuclear leucocytes. These granules appear to take up only the basic part of the tricolor mixture.

For Neusser's conclusions regarding the meaning of these granules, the reader is referred to pages 274 and 351. The researches of Futcher have in my opinion utterly disproved Neusser's claims. The granules are of no known clinical significance and certainly have no direct relation to gout or any other alloxuric diathesis. I have a triple stain (not made up for the purpose) which brings out Neusser's granules in every blood, normal or abnormal.

<sup>&</sup>lt;sup>1</sup> Wien. klin. Woch., 1894, No. 39.

# APPENDIX B

Table of 402 Blood Examinations in 121 Cases of Pernicious Anæmia.

				HE BLOC	
Remarks.			٠		
De- formi- ties.				+	++
Diameter.				#	1
Megalo- blasts.				:	: :
Normo- Nolasts.				Seen.	::
Per cent myelocytes.				:	::
Per cent eosinophiles.				:	::
Per cent lymphocytes.					::
Per cent polynuclears.				:	::
Number of leucocytes counted.				:	::
Per cent hæmoglobin.				:	35 30 37 35-40 35-40
White cells.	2,000	Normal.	Normal.	Dimin.	6,000 119,000 10,000 10,000
Red cells.	2, 211, 150 2, 755, 000 1, 220, 000 1, 240, 000 2, 211, 750	2,262,000 630,000 564,000 564,000	532,000 1,288,000 1,010,000	1,768,000	2,320,000 2,334,000 2,458,000 1,500,000 1,460,000 1,630,000 1,850,000
Date.	July 8th, 1885 Sept. 7th 10th, 1888 11th 99d		Nov. 3d July 7th, 1886 Aug. 8th, 1885	1886	25th Coct. 24th Mar. 31st, 1888 Oct. 25th, 1889 Nov. 4th 18th 18th 25th
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2,560,000 3,710,000 2,200,000 3,500,000 1,910,000	1,260,000	2,000,000 1,200,000 1,800,000 1,40,000	622, 160 812, 800 Dimin. 1, 226, 284 786, 000	793,777 960,000 1,300,000 1,368,000 821,600	1,304,000 1,416,000 1,320,410 680,000 992,593	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
1890	1891	1892	1892	1893		[w o]
8th 5th, 1st, 17th 10th 13th	15th, 15th		24th 27th 27th, 1 6th, 1	9th, 19th 4th 25th 6th 19th	Mar. 15th, 1894 After massage. One hour after. May 22d, 1893 May 3d	8th 16th 5th * N
Dec. Jan. Feb. May June Aug.	Sept. Oct. Feb.	May May Mar.		Feb. Mar. July	May May May	June
20	901	11 23 23	41		15 16	17

 $*\,\mathrm{No}$  whites seen while counting reds.

Table of 402 Blood Examinations in 121 Cases of Perincious Anæmia (Continued).

Remarks.	
De- formt- ties.	+ + + + + +
Diameter.	
Normo- Megalo- blasts. blasts-	13 13 18 18 18 18 18 18 18 18 18 18 18 18 18
Normo- blasts.	Man y.
Per cent myelocytes.	: એએનું : એનુંએ 
Per cent eosinophiles.	
Per cent lymphocytes.	
Per cent polynuclears.	
Number of leucocytes counted.	2000 : : : : : : : : : : : : : : : : : :
Per cent inidolgomæd	20852488 8044 : : : : : : : : : : : : : : : : : :
White cells.	1,000 1,000 3,000 3,000 1,000 7,500 7,500 13,000 13,000 13,000 13,000 11,000 5,200 8,000 10,000 8,000
Red cells.	1,137,040 1,250,000 1,550,000 1,500,000 1,500,000 1,500,000 1,500,000 1,500,000 1,500,000 1,500,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,000 1,288,
Date.	Oct. 2d 2d 12th 15th Jan. 10th, 1894 Jan. 10th, 1894 Jane 19th May 16th May 16th July 30th Aug. 15th June 5th June 5th J
No.	81 19 20 30 30 30 32 32 32 32 32 32 32 32 32 32 32 32 32

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55 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	588.24 58.36	24 82 82 0 0 88 83	0 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	25.00	<b>455</b>	32 52 32 52 32 52 32 52	35	ling nu
1,200 1,200 1,200 4,000 3,000	4,000 10,400 4,800	1,600	9,600 8,800 8,520 4,400	5,000	12,500 5,100 5,330 6,00	2,400 1,800 1,200 400	4,000 4,828 20,000	rith divid
1,064,000 1,584,000 2,312,000 1,536,000 3,648,000 3,840,000 3,840,000	3,200,000 1,248,000 1,552,000	1,088,000 1,168,000 1,136,000 865,000 1,092,000	2, 992, 000 1,824, 000 1,632, 000 1,752, 000	2,496,000 3,556,000 2,888,000	600,000 962,000 1,028,000	1,800,000 1,420,000 1,508,000 1,534,000	2,868,000 1,066,524 1,582,000	* Also thirteen red cells with dividing nuclei seen
	1895		1894		1895			irteen
31st 4th 113th 119th 25th 1st 7th 20th	13th 28th, 1st	8d 6th 23d 27th 30th	8th, 17th 13th 19th	szd 3d 17th		.g. 28th 2d 12th 15th	24th 7th 28th	Also th
Sept.	Nov. Aug. Sept.		Oct. Nov.	Dec.	Jan., Apr. 30th May 3d	Jan. Feb.	May	*
			36	į	28 28	300	33	

\* Also thirteen red cells with dividing nuclei seen.

Table of 402 Blood Examinations in 121 Cases of Pernicious Anæmia (Continued).

Remarks.	
De- formi- ties.	+ ‡+ ‡‡
Diameter.	+
Normo- Megalo- blasts. blasts.	004 013
Normo- blasts.	000 ::
Per cent myelocytes.	6
Per cent eosinophiles.	-3
Per cent lymphocytes.	4.66 39.05 39.05 57.6 53.05 53.05
Per cent polynuclears.	
Number of leucocytes counted.	400 78 400 53 1,000 53 500 57 500 67 800 67 800 67
Per cent hæmoglobin.	888888884 88 1 01108846 8888 84
White cells.	117.00 127.00 127.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00 120.00
Red cells.	1,634,000 3,396,000 3,296,000 3,500,000 3,508,000 3,508,000 1,400,000 1,384,000 1,384,000 2,336,000 2,336,000 4,500,000 4,500,000 1,696,000 1,144,000 1,096,000 1,096,000 1,096,000 1,096,000 1,096,000 1,096,000 1,096,000
Date.	Jume 4th 10th 17th 24th 17th 24th 10th 17th 21st 21st 24th 21st 28th 28th 28th 28th 28th 28th 28th 28t
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3,000	5,000	7,600	5,800	8,750	6,750	8,500	6,500	4,200	6,700	3,600	4,000	3,890	4,000		7,500	7,000	5,000	4,000	1,000	2,800	2,930	1,320	Normal.	1,000	1,800	10,100	34,000	4,200	4,100	4,400	2,331	3,463	2,464
1,752,000	2,224,000	988,000	2,524,000	1,164,000	1,280,000	1,184,000	896,000	590,000	430,000	1,984,000	936,000	598,000	1,336,000	956,000	1,800,000	1,768,000	1,996,000	670,600	490,000	1,344,000	976,000	758,000	Much.	1,126,000	1,627,000	1,819,000	2,500,000	1,288,000	1,212,000	1,464,000	1,628,000	1,852,000	1,984,000
											1896												1896										
5th	18th	10th *	16th	30th	19th	31st	3d	10th	23d*			15th	13th	26th	26th	8th	16th	11th	12th	15th	27th			11th		61	23d	9th	14th	18th	22d	26th	30th
Dec.					Jan.					Nov.						Mar.		April				May			June,	Sprin	June	July	,				
38		39	40				41			43			43		44				46	47			48					52					

Day of death.

Table of 402 Blood Examinations in 121 Cases of Pernicious Anæmia (Continued).

Remarks.	
De- formi- ties.	+++++ + 55 +
Diameter.	++ ++
Megalo- blasts.	20
Normo-I blasts.	
Per cent myelocytes,	5. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1.
Per cent eosinophiles.	400 in
Per cent lymphocytes.	<u>α</u> ω ω ω σ
Per cent polynuclears.	69     38       80     39       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80     30       80
Number of leucocytes counted,	500 500 500 500 500 600 700 700 700 835 835 835 835 835 835 835 835
Per cent hæmoglobin.	:: + :: 48888888888888888888888888888888
White cells.	Normal. 8, 200 6, 400 6, 400 6, 400 8, 450 8, 500 6, 200 6, 200 8, 500 6, 200 8, 500 8, 700 8, 700 8, 300 8, 30
Red cells,	1,150,000 1,280,000 1,640,000 1,640,000 1,312,000 1,170,000 880,000 1,104,000 664,000 1,280,000 1,104,000 1,104,000 1,240,000 1,240,000 1,240,000 1,240,000 1,492,000 1,492,000 1,492,000 1,492,000
Date.	July, Oct. 9th 23d 30th Nov. 20th Feb. 27th, 1897 39th Mar. 7th 23d 31st April 10th May 4th 16th 24th 30th 16th 27th 18th 27th 18th 28th 28th 28th 28th 28th 28th 28th 2
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70. 58.	48.446.8 40.56. 65.33.4 53.338.1 48.47. 66.231.4	550. 771. 69.	67.3 28 63.8 35. 66.6 30	54. 43. 55.4 41. 52.3 42. 12.8 81.
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3,200 6,000 8,000 1,700 2,800		2,300 5,500 4,400 8,000 4,200	6,300 37,000 36,000	3,300
1,192,000 3,820,000 984,000 1,680,000 1,376,000	1,946,900 963,000 503,000 363,000 1,296,000	1,248,000 1,364,000 1,920,000 1,632,000 1,520,000 1,180,000	1, 296, 000 1, 516, 000 1, 916, 000 1, 602, 000 1, 508, 000 1, 868, 000 2, 112, 000	2, 192,000 3,200,000 1,000,000 1,544,000 2,820,000
			1898	1898
20th 29th 19th 19th 5th 6th	12th 15th 22d 9th 20th 14th	19th 28th 11th 14th 18th 8th 19th	7th 1st 13th 20th 28th 12th, 20th 22d	9th, 9th, 21st 5th 10th 14th
Aug. July	Sept.	Aug. May June Nov.	Dec. Jan.	April Feb. Mar.
63	65 66 67 68	69 70 71	73 73	74 75 76

Table of 402 Blood Examinations in 121 Cases of Pernetous Anemia (Continued).

Remarks.	
De- formi- ties.	+2+ 2+2 22222++++ +
Diameter.	
Megalo- blasts.	8 :4 52 5 5 EEEEE ET 8 FE E
Normo-1	:: ಚಕಾಣ ಅವರಜನನಾಶರ : ದ
Per cent myelocytes.	
Per cent eosinophiles.	4.0001 0.11.11 1.1.1.000000 1.0 1.
Per cent lymphocytes.	75.2 66. 29.8 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67.2 67
Per cent polynuclears.	25.00
Number of lencocytes counted.	200 200 200 200 200 200 200 200 200 200
Per cent hæmoglobin.	8 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6
White cells.	\$\$,000 \$\$,000 \$\$,000 \$\$,000 \$\$,000 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$,100 \$\$
Red cells.	1,396,000 984,000 1,486,000 2,108,000 1,440,000 1,440,000 1,440,000 1,440,000 1,460,000 1,300,000 1,300,000 1,300,000 1,300,000 1,300,000 1,300,000 1,300,000 1,300,000 1,100,000 1,100,000
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Table of 402 Blood Examinations in 121 Cases of Pernicious Anæmia (Continued).

Remarks,	Mast cells, 6.6%.  Mast cells, 3.8%.  Red cells abnormally fragile and broken in spreading despite care.			
De- formi- ties.	+ + 1:+1+		+	+++
Diameter.	+ + + +++	:	+	+++
Normo- Megalo- blasts. blasts.	113 66 66 66 66 66 66 66 66 66 66 66 66 66	17	4	e :-
Normo- blasts.	1 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	17	:	- :-
Per cent myelocytes.	සු ස	1.	:	4. : <sub>0;</sub>
Per cent eosinophiles.		4.6	જાં	% % 4 4 .4
Per cent lymphocytes.	200 00 00 00 00 00 00 00 00 00 00 00 00	12.	11.	20.8 34.8 29.4
Per cent polynuclears,	460173644864848484848484848484848484848484848	71.	56.541.	76.8 20. 63.8 34. 66.4 29.
Number of leucocytes counted.	1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000 1,000	200	200	200
Per cent hæmoglobin.	080 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	: :	17 36 35	33 21 19
White cells.	22,400 1,200 8,600 6,700 2,600 11,000 8,600 10,000 10,000 11,500 11,500	13,000	4,900	6,600
Red cells.	1.278,000 828,000 783,000 956,000 1.110,000 1.890,000 2.012,000 2.012,000 1.380,000 2.000,000 2.830,000 2.830,000 2.830,000 3.600,000 3.600,000 3.600,000 3.600,000	3,430,000 2,756,000 3,575,000	1,120,000 1,220,000 1,732,000	1,672,000 1,008,000
Date.	May 1st 16th 16th 17th 15th 22d 25th 19th Aug. 1st July 22d 38th Aug. 3d Aug. 3d 12th 25th 25th 25th 25th 25th 25th	Sept. 5th Nov. 28th Dec. 26th		19th 8th 13th
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Mast cells, .8%. Mast cells, .8%. Mast cells, 1 &		Mast cells, 4%.			Mast cells, $0.8\%$ .
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33.25 23.25 23.25 23.25 23.25	0 00 00 00 0 00 00	86.8 86.8 87.7 8.4 8.4 8.4	85.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50 9.50	72.22 72.22 72.22 66.64 66.64 770 770 69.44 69.44 69.44	65.4 70.2
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Sept.	Nov.			Feb. Mar. Apr. Oct.	Dec.
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Table of 402 Blood Examinations in 121 Cases of Pernicious Anæmia (Continued).

k	SIECIAL TATHOLOGI OF THE BLOOD.	
Remarks.	Oval shaped red cells	forms.
De- formi- ties.	\vec{\zi}{\zi} \vec{\zi}{\zi} \vec{\zi}{\vec{\zi}} + + + + + + + + + + + +	
Diameter.	+++++++	
Megalo- blasts.		
Normo -	: a   :   - a	
Per cent myelocytes,		
Per cent eosinophiles.	- 1 : 1 : 1 : 2 : 1 : 1 : 2 : 2 : 2 : 2 :	
Per cent lymphocytes.	855.74 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 87.75 8	_
Per cent polynuclears.	79. 14. 14. 14. 14. 14. 14. 14. 14. 14. 14	
Number of leucocytes counted.	200 200 200 200 200 200 200 200 200 200	
Per cent hæmoglobin.	20 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
White cells.	元 3 8 8 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	
Red cells.	3,580,000 1,024,000 1,532,000 1,532,000 1,908,000 1,908,000 1,704,000 1,704,000 1,704,000 2,706,000 1,808,000 2,880,000 1,568,000 1,568,000 1,568,000 1,568,000 1,568,000 1,576,000 1,576,000 1,576,000 1,576,000 1,576,000	
Date.	Dec. 19th Apr. 35th Aug. 10th 20th 20th 20th 20th 20th 20th Aug. 25th Oct. 15th Nov. 11th Nov. 11th Nov. 11th Nov. 11th Nov. 25th 1st day 60th " 60th " 12th " 18t day 6th " 33tl " 33tl "	
No.	1114 115 117 118 119 120	

#### APPENDIX C.

Table Showing Gradual Increase in Size of Red Cells during Convalescence of Chlorosis.

Case I.

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		Per	Color	RED CELLS—DIA					Who was a su
	cent. Hgb.	cent. index	5.6 μ.	7.0 μ.	8,9 μ.	9.8 μ.	Aver- age.	Therapeu- tics.	
				p. ct.	p. ct.	p. ct.	p. ct.	p. ct.	
May 16th 17th	$\begin{vmatrix} 4,950,000 \\ 5,247,000 \end{vmatrix}$		0.46	5.0	64.0	31.0	1.0	7.46	Ovarian
June 8th	5,717,000	44	0.46	1.5	59.5	37.0	2.0	5.55	extract.
15th	5,740,000		0.59	1.0	52.5	41.5	5.0	7.71	1
23d $30th$	$\begin{bmatrix} 6,332,000 \\ 6,030,000 \end{bmatrix}$		$\begin{bmatrix} 0.57 \\ 0.60 \end{bmatrix}$	$\begin{vmatrix} 4.0 \\ 2.5 \end{vmatrix}$	$48.5 \\ 41.0$	$\frac{42.5}{49.0}$	5.0 7.5	$7.68 \\ 7.85$	Blaud's
July 7th	6,375,000	65	0.60	3.5	38.5	52.5	5.5	7.84	pill.
17th	5,730,000 5,687,000	$\begin{array}{ c c }\hline 70 \\ 72 \\ \end{array}$	$\begin{bmatrix} 0.72 \\ 0.75 \end{bmatrix}$	3.5	41.0	53.0 52.5	$\frac{2.5}{2.0}$	7.76 7.77	
26th Aug. 10th	$\begin{bmatrix} 5,087,000 \\ 5,792,000 \end{bmatrix}$		0.73	1.0	44.0	32.3	2.0	1.11	The state of the s
	, -,,						,	, , , , , ,	117
CASE II.									
May 29th	3,900,000		0.45	0.5	56.5	43.0		7.44	]
June 18th 25th	4,398,000 4,740,000	43 49	$0.56 \\ 0.61$	2.5	$51.5 \\ 49.0$	$\frac{44.5}{47.5}$	$\frac{1.5}{2.0}$	7.64	Ovarian extract.
July 2d	4,730,000		0.59	2.0	48.5	48.5	1.0	7.68	extract.
9th	5,884,000	57	0.58		38.0	53.0	9.0	7.99	j
Aug. 4th	$\begin{bmatrix} 5,667,000 \\ 6,437,000 \end{bmatrix}$	65 71	$0.67 \\ 0.65$	$\begin{array}{c c} 2.0 \\ 1.5 \end{array}$	$\frac{38.5}{39.0}$	52.0 54.0	$7.0 \\ 10.5$	7.91 7.94	Blaud's pill.
17th	6,040,000	71	0.69	1.5	31.0	59.0	8.5	8.04	pin.
	, ,	Į.	1		1	l	1	1	117
				CASE	III.				
Oct. 17th	3,701,000		0.43	2.0	68.5	29.5		7.37	
24th	4,855,000		0.47	1.0	61.5	34.0	3.5	7.55 7.74	Blaud's
Nov. 12th	5,230,000 6,021,000	53 72	$0.60 \\ 0.71$	2.0	$\frac{47.5}{39.0}$	$45.5 \\ 59.5$	5.0	7.97	pill.
20th	6,205,000		0.76	1.0	18.0	72.0	9.0	8.24	}
					'	'	'	•	.,
				CASE	IV.				
Dec. 12th	4,255,000		0.56	1.5	63.0	35.5		7.48	Blaud's
Jan. 13th	6,105,000 6,066,000		$0.63 \\ 0.69$	2.0	52.0 36.5	44.5 60.0	3.5	7.72 7.80	pill.
an. 19th	0,000,000	11	0.00	2.0	00.0	1 00.0	1.0	1.00	11/

#### APPENDIX D.

#### THOMAS R. BROWN'S FIRST CASE OF TRICHINOSIS.

SHOWING TOTAL NUMBER AND PERCENTAGE OF VARIOUS KINDS OF LEU-COCYTES.

Date. Leuco- cytes.		PERCENTAGE OF VARIOUS FORMS OF LEUCOCYTES.				NUMBER OF THE VARIOUS FORMS PER C.MM.			
	P. M. Neut.	S. Monos.	L. M. and T.	Eos.	P. M. Neut.	S. Monos.	L. M. and T.	Eos.	
Mar. 5th	17,000	55.0	3.0	5.0	37.0	9,350	510	850	6,300
$6 \mathrm{th}$	16,500	50.0	5.0	7.0	38.0	8,250	825	1,120	6,120
$7 ext{th}$	17,500	53.0	3.0	7.4	36.4	9,275	525	1,200	6,300
8th	25,300	60.9	1.9	5.9	31.4	15,000	500	1,500	7,750
$9 \mathrm{th}$	22,300	70.8	2.0	4.5	22.7	15,300	440	900	5,060
$10 \mathrm{th}$	16,500	74.7	3.1	8.0	15.1	12,000	480	1,280	2,400
11th	21,167	75.1	2.8	2.4	18.6	15,800	630	500	3,700
<b>12</b> th	17,500	77.8	4.4	3.0	15.1	13,600	770	510	2,625
13th	18,833	77.6	2.1	3.7	16.6	13,860	380	710	3,000
$^{1}4 h$	13,800	74.6	4.3	4.0	14.9	10,300	580	560	2,100
$15 \mathrm{th}$	13,750	74.0	7.6	3.2	13.6	10,300	1,000	420	1,720
16th	13,250	78.7	5.3	2.1	13.8	10,400	680	270	1,700
$17 \mathrm{th}$	16,000	73.2	11.3	1.9	13.5	11,700	1,770	310	2,160
18th	17,750	77.4	10.9	1.7	10.0	13,800	1,970	300	1,775
19th	20,400	71.1	13.1	2.3	13.1	14,200	2,600	460	2,600
$20  ext{th}$	15,700	76.5	10.1	2.2	11.2	12,100	1,570	340	1,760
21st	16,800	72.9	13.2	1.8	12.1	12,400	1,210	320	2,040
<b>2</b> 2d	14,000	79.2	10.8	1.7	8.3	11,200	1,540	240	1,130
23d	16,800	73.6	10.4	1.6	13.5	12,400	1,700	270	2,200
$24 \mathrm{th}$	19,600	74.6	11.2	1.8	11.2	14,800	2,200	360	2,200
25th	17,600	80.4	8.9	1.6	8.7	14,400	1,600	290	1,560
26th	24,000	69.2	12.7	2.0	15.4	16,800	3,120	480	3,700
27th	20,300	69.9	11.2	2.2	16.0	14,000	2,240	440	3,200
28th	24,100	68.3	10.1	2.4	18.9	16,300	2,400	580	4,560
29th	20,700	69.4	5.7	1.4	22.9	14,000	1,180	300	4,600
30th	22,300	60.7	9.6	3.0	26.0	13,400	2,200	670	5,720
31st	22,200	57.4	11.2	3.2	27.8	12,600	2,500	680	6,160
Apr. 1st	24,300	60.7	7.9	3.4	27.8	14,400	1,920	840	6,720
2d	23,800	59.3	11.6	3.0	25.0	14,100 13,300	2,760	710 700	5,950
3d	25,200	53.3	13.3	2.8	$\frac{30.0}{32.8}$	11,700	3,300	710	7,500 $7,590$
4th	23,400	49.9	13.3	3.0 4.0	33.8	10,100	$3,200 \\ 3,150$	960	7,160
5th	24,300	48.8	13.2	$\frac{4.0}{3.6}$	31.6	10,100 $12,700$	$\frac{3,100}{3,500}$	650	7,900
6th 7th	24,700	51.2 48.4	$14.0 \\ 14.5$	$\frac{5.0}{2.5}$	33.7	12,100	3,600	625	8,600
8th	$\begin{vmatrix} 25,100 \\ 29,600 \end{vmatrix}$	45.2	11.6	$\frac{2.3}{4.0}$	38.8	13,500	3,450	1,180	11,600
9th	28,900	45.0	13.3	3.2	38.3	13,000	3,850	930	11,000
10th	24.500	45.8	12.2	3.8	38.0	11,300	3,100	900	9,300
11th	29,800	42.2	14.0	4.0	39.8	12,600	4,150	1.180	11,900
12th	28,000	44.0	14.8	2.5	38.7	12,300	4.150	700	10,800
13th	24,200	42.0	11.8	1.4	44.2	10,000	2,880	340	10,700
14th	33,300	38.6	13.2	3.8	44.0	12,800	4,400	1,300	14,700
15th	28,100	34.8	19.6	1.6	44.0	8,600	5,550	450	12,300
16th	25,400	30.4	16.8	3.0	49.6	7,600	4,200	750	12,400
17th	27,000	31.8	13.2	3.4	51.2	8,600	3,500	920	13,700
18th	35,700	27.2	14.4	3.8	54.6	9,700	5,140	360	19,500

Date.	Leuco- cytes.	PERCENTAGE OF VARIOUS FORMS OF LEUCOCYTES.				NUMBER OF THE VARIOUS FORMS PER C.MM.			
		P. M. Neut.	S. Monos.	L. M. and T.	Eos.	P. M. Neut.	S. Monos.	L. M. and T.	Eos.
Apr. 19th	29,000	26.6	12.0	3.6	58.2	7,700	3,480	1,040	16,90
20th	19,200	22.2	12.4	4.2	61.0	4,200	2,350	800	11,60
21st	23,000	16.6	16.0	3.8	63.6	3,800	3,680	870	14,60
22d	26,600	10.4	18.8	7.4	63.4	2,700	4,900	1,950	16,50
23d	17,700	6.6	19.6	5.2	68.2	1,170	3,400	880	11,07
$24 \mathrm{th}$	18,800	7.2	23.4	4.4	64.8	1,370	4,400	840	12,20
25 th	15,600	8.8	19.2	7.2	64.8	1,370	2,990	1,020	10,40
$26 \mathrm{th}$	17,000	12.4	14.2	6.0	67.4	2,100	2,410	1,020	11,45
$27 \mathrm{th}$	12,000	20.0	8.6	7.4	64.0	2,400	1.030	890	7,70
28th	11,100	18.2	17.6	7.2	57.0	2,020	1,950	800	6,33
$29 \mathrm{th}$	12,800	19.4	19.4	6.8	54.4	2,470	2,480	870	6,99
$30  ext{th}$	13,200	20.8	17.2	8.2	53.8	2,700	2.270	1.080	7,02
Iay 1st	11,000	21.8	16.0	12.0	50.2	2,400	1,760	1,320	5,52
2d	8,900	27.4	17.8	8.4	46.4	2,440	1,580	740	5,16
3d	10,700	36.8	15 0	6.8	41.4	3,940	1,600	710	4,43
4th	10,700	34.8	20.8	6.4	38.0	3,720	2,120	680	4,07
5th	11,000	45.6	19.0	6.6	28.6	5,020	2,090	710	3,15
6th	10,300	41.0	20.2	4.8	33.6	4,220	2,080	490	3,46
7th	12,300	50.8	20.2	6.0	23.0	6,250	2,480	740	2,83
8th	11,500	54.0	18.0	4.0	24.0	6,210	2,070	460	2,76
9th	11,500	59.8	17.6	6.2	16.4	6,850	2,020	710	1,89
10th	15,700	51.0	12.8	5.6	20.4	7,100	2,010	880	3,20
11th	13,500	62.4	14.2	4.8	18.8	6,420	1,920	650	3,54
12th	11,000	64.0	14.4	4.8	16.8	7,040	1,580	530	1,85



## BIBLIOGRAPHY.

It has seemed to me best to give a list only of the books and articles which I have found most useful, since the general bibliography of the subject is now large enough to form a volume by itself. Most of the larger works here described contain extensive bibliographies—especially that by Ewing.

#### Text-Books.

1. Ewing: "Clinical Pathology of the Blood," Philadelphia, 1901, 8vo, 432 pages (Lea Bros.). This is the newest book on the blood and the fullest discussion of the theoretical points connected with diseases of the blood. The bibliography and résumé of the work of other observers contained in each section are admirable. The original observations of the writer are contained chiefly in the chapters on malaria and diphtheria. The tone of the book is admirably sane and judicial throughout. The illustrations are poor.

2. Ehrlich, Lazarus, Pinkus, and v. Noorden in vol. viii. of Nothnagel's "Specielle Pathologie und Therapie," issued between 1898 and 1901 (Wien, Hölder & Co.) have written a series of articles on anæmia, leukæmia, and chlorosis, which together amount to many pages 8vo. The clinical aspects and therapeutics of the diseases are included. The hæmatology of the book is on the whole inferior to Ewing's, although parts of it, especially v. Noorden's study of chlorosis, are masterly. The articles on anæmia are interesting as they contain Ehrlich's latest utterances. The work is out of date in some respects owing to its characteristically Teutonic ignorance of important work done in England and America, but it is undoubtedly the standard German work on the subject.

3. Hayem: "Du Sang," Paris, 1889, 8vo, 1035 pages (French). This valuable book is the largest that I know of on the subject, and contains a mine of information on the morphology of the blood in health and disease, mostly from the author's own experience, literature being but little referred to. It contains a comparative anatomy of the blood and a long account of blood development. Unfortunately, it is dominated throughout by a theory of blood formation which has never gained acceptance by any other authority. It is very full on the subject of fibrin formation and of chlorosis. The illustrations are excellent. In a later work, "Leçons sur les Maladies du Sang," Paris. 1900, 8vo, 700 pages (Masson et Cie.), Hayem has brought his previous book in a measure up to date, but the "Leçons" are very diffuse and wordy and

contain but a small fraction of the original work for which Hayem's first book was so notable.

4. v. Limbeck: "Grundriss ein. klin. Pathologie des Blutes," Jena, 1896, 8vo, 383 pages (Fischer). The second edition of this book, which appeared in February, 1896, is more than twice the size of the first edition (1892)—a fact illustrating the rapidity of the subject's growth. It is on the whole the best general text-book known to me, being equally full on all parts of the subject, including, for example, technique (which Grawitz omits) and of the chemistry of the blood, which is at present the author's special interest and on which Havem is meagre. The illustrations are poor and the type is trying to the eyes. The writer shows little personal experience with the morphology and micro-chemistry of the blood, and this is the weakest side of the book. A large part of the book is concerned with the physiology of the blood.

5. Grawitz: "Klinische Pathologie des Blutes," Berlin, 1895, 8vo, 333 pages (Enslin). Issued in April, 1896. This book is largely devoted to the matter indicated by the title and contains no account of blood technique, and only thirty pages on the normal anatomy and physiology of the blood, while two hundred and seventy concern the blood in disease. The arrangement of the book is very clear and helpful. The author's main interests are in the estimation of the dried residue of the blood in various diseased conditions and in the bacteriology of the blood, so that the book is specially full on these topics. The illustrations are poor. Type and paper are excellent.

6. Coles: "The Blood: How to Examine It," etc., London, 1898 (J. and A. Churchill), 8vo. A clear and fairly complete account of the work of others upon the subject. Especially full on technique.

These are the best text-books known to me on the whole subject. Taylor's masterly monograph, entitled "Studies in Leukæmia" and forming part of the volume of "Contributions from the William Pepper Laboratory of Clinical Medicine" (Philadelphia, 1900), contains within its one hundred and seventy-eight quarto pages not merely an unrivalled account of leukæmia but a great deal of important matter on leucocytosis, anæmia, and most other hæmatological topics. It is by far the best study of leukæmia known to me in any language.

### Treatises on Special Portions of the Subject.

1. Reinert's "Die Zählung der Blutkörperchen," Leipzig, 1891 (Vogel), 246 pages, is an admirable account of the avoidable and unavoidable errors in blood examination, and the best methods of reducing error to a minimum. A number of careful examinations of the blood in health and in various diseases are also given; and an outline of the scope of blood diagnosis closes the book.

2. Türk's monograph on the "Condition of the Blood in Acute Infectious Disease" is an admirable résumé of German and French literature on the subject, together with a detailed study of fifty-two cases. Published at Wien and Leipzig, 1898 (Braumüller), 347 pages, 8vo.

- 3. Rieder's "Beiträge zur Kenntniss der Leukocytosis," Leipzig, 1892 (Vogel), 220 pages, is an admirable work in all respects, although now considerably out of date. It shows, as very few of the foregoing treatises do, a practical acquaintance, on the author's part, with the details of blood morphology and microchemistry. A very large number of blood counts in many diseases are recorded.
- 4. Löwitt's "Studien zur Physiol. und Pathol. des Blutes u. der Lymphe" (Jena, 1892 [Fisher], 8vo, 138 pages) is mostly concerned with experiments on animals and intended to throw light on the theory of leucocytosis. The conclusions of the book have not been generally adopted, though its facts have been mostly verified.
- 5. Theyer and Hewetson's book, on the "Malarial Fevers of Baltimore," leaves nothing more to be desired in that direction. It is two hundred and fifteen pages long, published by the Johns Hopkins press of Baltimore in 1895. It contains a summary of the literature of the subject, an analysis of six hundred and sixteen new cases, and some admirable colored plates. It is a model of its kind in every respect, and an ideal for others to aim for. Essentially the same material is reorganized in Thayer's "Lectures on the Malarial Fevers," New York, 1899, Appleton.
- 6. Ehrlich's "Farbenanalytische Untersuchungen" (Berlin, 1891 [Hirschwald], 137 pages) contains nine short essays by Ehrlich and three by his pupils. Considering the reputation of the writer they are at the present day rather disappointing reading, and contain little that is not better expressed elsewhere.
- 7. Weiss's "Hæmatologische Untersuchungen" (Wien, 1896 [Prochaska] 112 pages, 8vo) contains many valuable studies on various points.

### Magazine Articles of Special Value.

- 1. On Concentration and Dilution of the Blood—Oliver: Lancet, June 27, 1896.
- 2. On Leucocytosis—Goldschneider and Jacob: Zeit. für klin. Med., 1894, vol. 25. Krebs: Inaug. Dissert., Berlin, 1893. Sadler: Fortschr. d. Med., Supplement-Heft, 1892. Also Klein, in Volkmann's Sammlung klinischer Vorträge, December, 1893, and of course Rieder and Türk above referred to.
- 3. On Anæmia—Dunin: Volkmann's Sammlung klin. Vorträge, 1896, No. 135. Romberg: Berlin. klin. Woch., June 28, 1897.
- 4. Parasitic Anæmia—Schaumann: Zur Kenntniss der sog. Bothriocephalus Anämie, Berlin, 1892, 214 pages; and Askanazy: Zeitschr. f. klin. Med., 1895, p. 492. Brown: Journal of Experimental Medicine, May, 1898 (Trichinosis).
- 5. Leukæmia—Fraenkel: Deutsche med. Wochenschrift, 1895, p. 639. Fraenkel: 15th Congress für inn. Medicin, Wiesbaden, 1897. Benda: *Ibidem.* Dock: Moscow Internat. Congress, 1897.
- 6. Pernicious Anæmia—Discussion by Birch-Hirschfeld, Ehrlich, Troje, and others, at the XI. Congress f. inner. Med. (Leipzig, 1892).
- 7. Pneumonia—Billings: Bulletin of the Johns Hopkins Hospital, November, 1894. Diphtheria—Billings: New York Medical Record, April 25, 1896.

Typhoid—Thayer: Johns Hopkins Hospital Reports, vol. iv., No. 1. Engel: 15th Congress für inn. Med., Wiesbaden, 1897. Exanthemata—Felsenthal: Arch. f. Kinderheilk., 1893, p. 78. Zappert: Zeitschr. f. klin. Med., 1893, No. 23. Smallpox—Pick: Arch. f. Dermatol. und Syph., 1893, p. 63. Sepsis—Roscher: Inaug. Dissert., Berlin, 1894. Cholera—Biernacki: Deutsche med. Wochenschr., 1895, No. 48. Diabetes—Bremer: Moscow Internat. Congress, 1897.

8. Syphilis—(a) Reiss: Arch. f. Dermat. und Syph., 1895, Hft. 1 and 2. (b) Justus: Virchow's Arch., 1895.

9. Tuberculosis—(a) Dane: Boston Medical and Surgical Journal, May 28, 1896. (b) Stein und Erbmann: Deutsche med. Wochenschrift, 1896, No. 56, p. 323. (c) Grawitz: Deutsche med. Wochenschr., 1893, No. 51.

10. Malignant Disease—Taylor (International Medical Magazine, July, 1897). (a) Sadler: Loc. cit. (b) Reinbach: Langenbeck's Archiv, 1893, No.

46. (c) Strauer: Dissert., Greifswald, 1893.

11. Bacteriology—Sittmann: Deutsches Arch. f. klin. Med., vol. 53.

12. Diseases of the Stomach (especially Cancer)—Schneyer: Zeitschrift f. klin. Med., 1895, p. 475. Osterspey: Inaug. Diss., Berlin, 1892.

13. Eosinophiles—Zappert: Zeitschr. f. klin. Med., 1893, vol. 23.

14. Hæmoconien-Müller: Wien. med. Presse, 1896, No. 36.

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